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FOREWORD

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____ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

____ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

____ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Thomas J. Eckfeldt 1/30/95

PI - Signature / Date

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13. ABSTRACT *(Maximum 200 words)*

This grant provides partial core support for the Institute of Laboratory Animal Resources (ILAR), which is a component of the Commission on Life Sciences (CLS), one of the principal operating units of the National Academy of Sciences (Academy). The Academy operates as a private, non-profit institution charged with providing advice to agencies of the federal government on matters of science and technology. ILAR provides information on the selection, care, and use of biologicals and animals used in research, testing, and education. ILAR's best known report, the Guide for the Care and Use of Laboratory Animals (Guide), was revised in 1994 to be published in 1995. Oversight for the work of ILAR is provided by ILAR Council, a standing committee of 15 scientists, veterinarians, and ethicists, which meets three times each year to review all aspects of ILAR's program and develop new initiatives. ILAR has two types of programs: core and special projects. This grant primarily supports the core program, consisting of the meetings and activities of Council and those of staff in the publishing of *ILAR News*, in the activities of the Animal Models and Genetic Stocks Information Program, and International Activities. Partial support is also provided for the development of special projects and convening of workshops.

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1994 Annual Report
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National Research Council
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INTRODUCTION

This grant provides partial core support for the Institute of Laboratory Animal Resources (ILAR), which is a component of the Commission on Life Sciences (CLS), one of the principal operating units of the National Academy of Sciences (Academy). Under an 1863 congressional charter, the Academy operates as a private, non-profit institution charged with providing advice to agencies of the federal government on matters of science and technology. Since 1952, ILAR has served this role in regard to the selection, care, and use of biologicals and animals used in research, testing, and education. ILAR's best known report is the *Guide for the Care and Use of Laboratory Animals* (*Guide*), of which preparation of the seventh edition was initiated during this grant year. ILAR consists of a staff of four to six depending on the nature of the work underway. Oversight for the work of ILAR is provided by ILAR Council and the CLS.

ILAR Council is a standing committee of 15 scientists, veterinarians, and ethicists, which meets three times each year to review all aspects of ILAR's program and develop new initiatives. John VandeBerg, Scientific Director, Southwest Foundation for Biomedical Research is the chairman of Council (see Appendix 1: ILAR Committee Rosters).

ILAR's work follows procedures prescribed in the charter of the Academy and operating procedures of the National Research Council (NRC), the administrative arm of the Academy. When federal agencies request the advice of the NRC, a series of events is set into motion that typically leads to published recommendations on the desired topic. The strength of this process is achieved by selecting and appointing a balanced committee of experts that produces a report

in accordance with NRC operating procedures. Separately appointed committees of experts provide anonymous reviews of each report. Staff supports and enables this process behind the scenes, which is a component of ILAR's core program.

BODY

ILAR has two types of programs: core and special projects. The core program includes the work involved with supporting ILAR's advisory council, maintaining ILAR's ongoing programs, and initiating and prioritizing ILAR's special projects. This grant supports the core program. Special projects are those accomplished by NRC-appointed volunteers who serve on NRC-appointed committees. All ILAR committees work under the auspices of the NRC, and are overseen by the CLS. Committee reports, which usually take 18 to 36 months to complete, are submitted for independent peer review. Reports are normally published by the National Academy Press. In 1994, 73 scientists, veterinarians, and medical ethicists served on ILAR committees (see Appendix 1: ILAR Committee Rosters).

I. Core Activities

A. **ILAR Council.** ILAR Council met three times in 1994 to review ongoing work and plan new activities: February 17-18 at the Arnold and Mabel Beckman Center, Irvine, California; July 25-26 at the J. Erik Jonsson Woods Hole Center Woods Hole, Massachusetts; and October 10-11 at the National Academy Sciences Building, Washington, D.C. The

Beckman and Woods Hole centers are study sites of the Academy and enable greater participation of west and east coast members, respectively. ILAR Council works under the general guidance of ILAR's Mission Statement:

> *The Institute of Laboratory Animal Resources (ILAR) develops guidelines and disseminates information on the scientific, technological, and ethical use of animals and related biological resources in research, testing, and education. ILAR promotes high-quality, humane care of animals and the appropriate use of animals and alternatives. ILAR functions within the mission of the National Academy of Sciences as an advisor to the federal government, the biomedical research community, and the public.*

The primary responsibility of Council is to review all ongoing activities. This is the main focus of council meetings and innumerable conference calls between meetings.

Council reviewed the progress of the following current committees during 1994. See below for project descriptions.

Occupational Health and Safety in Care and Use of Research Animals

Psychological Well-being of Nonhuman Primates

Revision of the Guide for the Care and Use of Laboratory Animals (Guide)

Rodents: Laboratory Animal Management Series

Dogs: Laboratory Animal Management Series

Council initiated or reviewed the activities of the following new projects during 1994. See below for project descriptions.

Workshop on Collection and Importation of Biological Materials, Animals, and Plants

Workshop on Biological Resource Databases

Workshop on the North American Free Trade Agreement (NAFTA)

Workshop to Examine the Appropriate Use of Animals and Their Alternatives in Education

Transgenic Animals: Benefits and Risks

The Cost of Research

Laboratory Animal Management series reports on *Swine, Ruminants*, and *Nonhuman Primates*

Expansion of *ILAR News* to *ILAR Journal*

In addition to the ongoing projects and new initiatives (see II. Special Projects), Council concentrated on the activities of the following three subcommittees of core activities.

B. ***ILAR News.*** *ILAR News* has developed and matured into a valuable resource for members of institutional animal care and use committees, veterinarians, institutional officials, biomedical researchers, and all those whose work involves the use of animals in research. To reflect this remarkable growth and to better convey the true nature of its present publication, ILAR will introduce *ILAR Journal* beginning with the Winter 1995 issue. The new *ILAR*

Journal will continue and expand the tradition of presenting thoughtful and timely scientific articles, commentary, and discussions on issues that impact the laboratory animal science community.

Since 1989, all articles in *ILAR News* have been peer-reviewed, and since 1991 issues have focused on themes chosen for their timeliness and appropriateness by the Editorial Panel. *ILAR Journal* will continue this approach, with theme issues planned through 1995 that include perspectives on xenotransplantation, a comparison of animal care systems in several countries, and a discussion of adjuvants and antibody production. These theme issues will not only incorporate articles solicited from experts all over the world, but will include additional elements, such as introductions and editorials from the ILAR Council and discussions of emerging issues. *Issues for IACUCs*, book reviews, abstracts from relevant conferences or symposiums, as well as announcements of news items of interest, meetings, and new books will continue as features of *ILAR Journal*.

In 1994, ILAR published 3 issues of *ILAR News*.

Winter and Spring 1994 are a two-part series on farm animals in biomedical research and include reviews of goats, swine, and transgenic farm animals in biomedical research, as well as articles in the *Issues for IACUCs* department on oversight of agricultural animals in biomedical research and on melding the guidelines for farm animals in biomedical and agricultural research.

Summer/Fall 1994, a combined issue (currently in press). In collaborated with the Michigan State University Genetics Program Symposium on Gene Therapy, ILAR offers reviews of gene therapy for metabolic diseases, arthritis, inherited neurological diseases, inherited myelin disorders, as well as abstracts from the Michigan State University Symposium.

The following issues are being prepared for 1995:

Winter 1995 will introduce *ILAR Journal*, beginning with *Perspectives on Xenotransplantation*, which will bring together varying viewpoints on controversial issues surrounding xenotransplantation including the infectious disease potential, immunological hurdles, and the right time to move from animal to human trials. It will also include a discussion of ethical issues surrounding the use of xenografts.

Spring 1995 will be an "international issue" prepared by six authors in different countries of the world with substantial experience with laboratory animals. It will provide a comparison of animal care legislation and policies among different countries of the world.

Summer 1995 will address humane and scientific considerations for adjuvants and antibody production, including discussions of oversight responsibilities.

Fall 1995 will include several manuscripts on husbandry and care of commonly used nonmammalian invertebrates in biomedical research.

C. **Animal Models and Genetic Stocks Information Program (AMGS).** Some of the most critical information needed by scientists is often the most difficult to obtain, including information that assists a scientist to select the most appropriate model for the proposed research and, if the model is an animal, to find sources of the model and provide appropriate care. For 40 years, ILAR has conducted a program to provide such information. That program, called the Animal Models and Genetic Stocks Information Program, offers assistance in locating sources of animals, selecting appropriate animal models, using standardized nomenclature, understanding the importance of the use of animals in biomedical and behavioral research and testing, and interpreting guidelines for the humane care and use of animals. It includes two databases: one (called Animals for Research) contains commercially available and investigator-held colonies of animals for research; the other is a registry of codes used with standardized nomenclature of rodents and rabbits to identify institutions that maintain breeding colonies. To answer questions, ILAR also draws on its library of reference material, including ILAR committee reports, and has access to several medical libraries. Although staff members do not do literature searches, they often assist investigators by suggesting appropriate key words to use in a literature search. Staff also draws on its own experience and expertise to provide information or refers queries to other experts, usually NRC committee members.

The AMGS Program is not currently advertised, because ILAR does not have the resources to handle the expected increase in requests. Nonetheless, the number of questions received have been substantially greater in the past 2 years than in previous years. During 1991 and 1992,

ILAR staff responded to 1,650 and 1,752 queries, respectively; during 1993, the number was 2,691; and during 1994, the number was 2,005. In May 1994, ILAR implemented a computerized system to more accurately track the number and kinds of requests received by the program. A summary of information for 1994 is presented in Table 1.

Table 1 Requests received by the AMGS Program During 1994

Type of Request	Number of Requests
Sources of Animals	
Mice	484
Rats	288
Other Mammals	195
Other Vertebrates	21
Invertebrates	4
Other Information on Animal Models	138
Nomenclature	101
Publications	487
Students	192
Other	95
TOTAL	2,005

Most of the inquiries are made by people in research institutions, including universities and hospitals (55%), federal research laboratories (8%), private research institutions (8%), and industry (15%); the remainder (14%) are from a variety of sources, including animal suppliers,

architects, congressional staff, law firms, and students. During 1994, 3,945 ILAR publications and packets of information for students were distributed free-of-charge, and another 1,300 ILAR reports were sold by the National Academy Press.

ILAR is planning to update and expand the Animals for Research database and make it available online in a user-friendly format. The components of the database will be as follows:

- *Listings of Sources of Laboratory Animals.* ILAR's in-house Animals for Research database includes commercially available and investigator-held colonies of laboratory animals in North America. ILAR plans to update this database and expand it to include international sources. Another important area for expansion is in nonmammalian models. Scientists are increasingly making use of lower vertebrates and invertebrates in such fields as embryology, developmental biology, toxicology, carcinogenesis, physiology, and aging. Some of the most commonly used are zebra fish (*Brachydanio serio*), medakas (*Oryzias latipes*), guppies (*Poecilia reticulata*), axolotls (*Ambystoma mexicanum*), African clawed toads (*Xenopus laevis*), squid (*Loligo* spp.), sea urchins (*Echinus* spp.), and fruit flies (*Drosophila* spp.). ILAR plans to expand its listings of sources of nonmammalian models and to include some nontraditional sources, such as pet-supply companies.

- *Catalogs and Registries of Animal Models.* Database catalogs and registries of animal models will be included. The goal is to provide assistance in choosing appropriate models by enabling scientists to search for diseases and characteristics of interest among a wide range of mammalian and nonmammalian animals. The format will be a brief description of each model,

accompanied by a list of key references. For mice, the database will make use of the catalog of mutants (Mouse Locus Catalog) already available in the Mouse Genome Database (MGD; formerly GBASE), the catalog of inbred mouse strains that will soon be available in MGD, and the listings of transgenic animals and animals with targeted mutations in TBASE (the database developed at Oak Ridge National Laboratory, Oak Ridge, Tennessee, and maintained at The Johns Hopkins University, Baltimore, Maryland). For rats, ILAR will work with the International Committee on Rat Nomenclature to develop catalogs of inbred and mutant rats. Communication with the committee will be by email with members and by attendance at the committee's meeting in Toulouse, France, in July 1996. For other species, ILAR will approach professional societies to involve them in developing animal-model registries. One such registry, the International Registry of Animal Models of Thrombosis and Hemorrhagic Diseases, has been published periodically in *ILAR News*, most recently in 1988 (W. J. Dodds, *ILAR News*, 30(1):R1-R-32, 1988). ILAR will use that registry as a model in its interactions with professional societies.

- *A Bibliography*. ILAR guidelines, other publications on animal care and breeding, and publications on animal models and genetic stocks will be provided.

- *A Bulletin Board*. To facilitate communication among users and between users and ILAR staff, a bulletin board will be made available. It will enable scientists to request information not in the database, identify new and novel stocks, and make comments on specific animal models. It will also assist in the preservation of unique animal models by enabling an

investigator to determine easily whether other colonies of the model exist and to advertise the availability of a colony that is about to be disbanded. This bulletin board, unlike many others available on the Internet, is not intended to be a mechanism for long communications between scientists. For that reason, ILAR staff will reserve the right to monitor and restrict the postings, if it becomes necessary.

- *Registry of Laboratory Codes*. The registry will be developed in a way that will allow users to assign themselves provisional codes electronically, with final approval by ILAR staff.

It is intended that the development and testing phase of the database will be completed in one year after federal funding is received. During the second year, the database will be made available to the public and its use tracked.

D. **International Activities.** The International Subcommittee of ILAR Council met three times in 1994, preceding each meeting of Council. ILAR's international activities mission statement for the Western Hemisphere is:

> *As a national resource for science-based policy development, ILAR will seek to establish a joint partnership with Canada (linked through NAFTA) for the dissemination of educational and training materials in Mexico. The goal of this activity is to assist in the development of regional self-reliance in health research. Mexico will serve as a model for follow-on activities in Central and South America and the Caribbean.*

For Asia and the Pacific Rim:

ILAR seeks to further the relationships with Japan through the U.S.-Japan Non-Energy Agreement and with the International Council for Laboratory Animal Science for the further development and refinement of animal models, the sharing of information and facilities, and the education and training of young scientists in developing countries.

For Europe:

ILAR seeks to work with European countries to assist with the harmonization of nontariff trade barriers, regulations, and the collection and transfer of biological materials.

In order to facilitate these liaisons, ILAR interacts with numerous organizations and agencies in the United States and foreign countries. Among these are the NRC/CLS joint programs with the Mexican Academy of Sciences, and the Pan American Health Organization, Fogarty International Center at NIH, Department of State, Centers for Disease Control and Prevention, Interagency Research Animal Committee, U.S. Agency for International Development, Canadian Council on Animal Care, Agriculture Canada, and various Mexican departments of animal health and agriculture. In addition, ILAR maintains close contact with U.S. scientific societies, pharmaceutical companies, biomedical investigators, veterinarians, and administrators. This network serves to alert ILAR of existing or anticipated international problems affecting

biomedical and biological research and biodiversity and to enable ILAR to better understand the broad needs of U.S. science in interacting with foreign organizations.

Electronic communication has greatly increased the ease and pace of international communication. The benefit of this is that potential problems can be identified quickly and interventions developed or solutions offered, often within a day. The problem with this rapid communication is that little-known (outside their country or association) organizations can develop, and circulate internationally, "draft" policy statements that rapidly become adopted and impose severe restrictions on U.S. science without benefit of U.S. involvement. Not infrequently the issue of global biodiversity is cited as a basis for restricting access to animal and plant species. While this is a notable concern, many times these cautions are raised and become obstacles to research without studies being conducted on the true impact of collections on animal and plant populations. ILAR continually monitors these developments and seeks to involve appropriate U.S. components at the earliest possible time. Many of these efforts approach an issue through a goal of avoiding a presumed risk, however slight. They do not assess the likelihood of a hazard associated with the risk, and often fail to recommend strategies to control the hazard. This expensive and time consuming risk avoidance strategy results in restricting transport or importation of biological models, imposes undue constraints on quarantine procedures, and generates unnecessary levels of concern for airline industry personnel, the public, and some officials. Through support of a number of NRC documents, ILAR stresses applying scientifically valid process of hazard identification and risk assessment to such

situations.

This activity resulted in ILAR's direct involvement in proposals to develop an international policy on animal care and use (by the International Council of Scientific Unions, ICSU), and an international standard on transport and quarantine on nonhuman primates. Both proposals were initiated outside the international laboratory animal science communities and are redundant or in conflict with existing U.S. policies. In 1994, a significant effort was directed to the planning of a NAFTA workshop in conjunction with the March 1995 meeting of ILAR Council. This workshop titled, *North American Free Trade Agreement: Impact on Biological and Agricultural Research and Trade* (see Appendix 3) will be held at the National Academy of Sciences Arnold and Mabel Beckman Center, Irvine, California on March 1, 1995. Representatives from Canada, Mexico, and the Unites States are invited to address the anticipated impact of NAFTA on U.S., Mexican, and Canadian biomedical research and agriculture. Depending on the outcome of these discussions, ILAR will plan additional activities to address specific issues as may be identified, e.g., collection and transport of biologicals, animals, and plants (see also II. Special Projects); marketing of pharmaceutical products; and intellectual property rights.

Although Canada and Mexico are the current focus of ILAR's attention in regard to NAFTA, activities in Japan, the Pacific Rim, and Europe remain important. As the U.S. member of the International Council on Laboratory Animal Science (ICLAS), ILAR is asked to participate and comment on a number of activities at the international level. One such activity involved the development of an international standard for quality control of laboratory animals.

As a result of ILAR's report *Rodents: Laboratory Animal Management Series* a committee on quality control has been established by ICLAS with a goal of achieving international standards for genetic and microbiological quality control of laboratory rodents. A meeting of members of ILAR Council and staff with U.S. and Japanese scientists was convened at the National Institutes of Health in 1994 under the U.S.-Japan Non-energy Agreement to discuss implementation of these recommendations.

In addition to the external activities, ILAR's international activity involves working closely with the AMGS and *ILAR Journal* subcommittees in numerous overlapping areas of interest, including database development and electronic communication, and initiation of a "Department" of international activities in *ILAR Journal*. In 1994, considerable attention was given by the International Subcommittee to the international issue of the *ILAR Journal* (Spring 1995). Forthcoming will be regular columns on international activity in *ILAR Journal*, and the coordination of international access to ILAR databases with the help of the AMGS subcommittee.

II. Special Projects

In addition to those areas discussed under I. Core Projects, this grant provides support for some of the activities of ILAR's Special Projects, the second primary focus of ILAR's activity. These projects normally evolve in one of two ways. The first way is when ILAR Council or another NRC component believes a workshop is needed to explore a specific topic to determine

whether more in-depth study should be undertaken. The *Workshop on Collection and Importation of Biological Material, Animals, and Plants*; *Workshop on Biological Resource Databases*; and *Workshop on North American Free Trade Agreement: Impact on Biological and Agricultural Research and Trade* are examples. Limited funds from the NRC are received for some of these planning activities, but it is always supplemented by core funds from this award. These workshops are discussed in more detail below.

The second way in which special projects evolve is through the recommendation of a workshop or through direct request of an agency or Congress. Most NRC special projects are conducted in order to provide advice to one or more federal agencies, and such is the case for the following ILAR's projects: Revision of the *Guide for Care and Use of Laboratory Animals (Guide)*; *Occupational Health and Safety in Care and Use of Research Animals*; *Psychological Well-being of Nonhuman Primates*; *Dogs: Laboratory Animal Management Series*; and *Rodents: Laboratory Animal Management Series*. Upon receipt of a request to provide guidance or recommendations, ILAR staff, with the assistance of ILAR Council and others, conducts a literature survey and writes a proposal. These proposals are then submitted to the sponsor(s). Upon receipt of funding, the normal method by which the NRC addresses such issues is to appoint an expert committee to author a report, the members of which serve without compensation. Much of the planning and preparation of these proposals is supported by core funds. Through the support of activities of ILAR Council, invited advisors, and the ILAR staff, core grants enable many of the planning and developmental activities that lead to special

projects. Following is a list of these special projects, including a summary of accomplishments during 1994 in each, and plans for the future.

A. **Revision of the *Guide for Care and Use of Laboratory Animals* (*Guide*).** The current edition of the *Guide* was last published in 1985. The normal 4-5 year revision cycle was delayed due to the 1985 passage of amendments to the Animal Welfare Act and the Health Extension Act of 1985 and to changes in technology in such areas as transgenic animals. In 1993, a grant was awarded from NIH as lead agency and the committee was appointed. Three public meetings were held in late 1993 and early 1994 in Washington D.C., San Francisco, and St Louis. Three other meetings were held in conjunction with national scientific meetings - American Association of Laboratory Animal Science (AALAS), Public Responsibility in Medicine and Research (PRIM&R), and Applied Research Ethics National Association (ARENA). In addition, the committee met for nine days in three sessions in 1994 (February 2-4, June 28-30, and November 2-4). These public meetings were important in order to receive comments and recommendations from as wide an audience as possible for revision of this important document. As a result of the requests received at these meetings, the NRC appointed an additional member (Mrs. Jo Ann Steggerda) to the committee to represent general community interests. Nevertheless, in 1994 a law suit was brought against the Department of Health and Human Services and the Department of Agriculture (two of the sponsors) alleging that the NRC process by which it appointed the committee and conducts its meetings is in violation of the

Federal Advisory Committee Act (FACA). At the Academy's request, it too became a defendant in the suit. The outcome of the suit is pending. The final meeting of the committee is planned for February 22-24, 1995, after which it will be edited, submitted for NRC report review by an independent NRC-appointed committee, and published by the National Academy Press in mid-1995. The committee roster is attached (see Appendix 1: ILAR Committee Rosters).

B. **Laboratory Animal Management Series.** As companions to the *Guide*, ILAR extensively revised two species-specific reports in the *Laboratory Animal Management* series. *Dogs: Laboratory Animal Management Series*, published in 1994, revises a 1973 report entitled *Dogs: Standards and Guidelines for the Breeding, Care, and Management of Laboratory Animals* and includes a new section on care and management of dogs characterized for specific research protocols. *Rodents: Laboratory Animal Management Series* revises and combines three earlier reports, *Laboratory Animal Management: Rodents* (1977); *Laboratory Animal Management: Genetics* (1979); and *Long-Term Holding of Laboratory Rodents* (1976). This report is in press. Copies of *Dogs: Laboratory Animal Management Series* are enclosed (see Appendix 2: ILAR Reports). Rosters of both committees are attached (see Appendix 1: ILAR Committee Rosters).

Plans continued in 1994 to revise three other Laboratory Animal Management reports on nonhuman primates, swine, and ruminants. Proposals for these reports have been submitted to several prospective sponsors. Committees will be appointed and the revisions will begin when funding is obtained. The selection and prioritization of these and other ILAR committee reports

originates with ILAR Council and represents one area in which core supported activities (Council) merge with special projects.

C. **Occupational Health and Safety in the Care and Use of Research Animals.** This committee met four times in 1994: January 12-14, April 7-10, June 2-3, and October 13-14. In addition, the committee presented a three-day forum for the American College of Laboratory Animal Medicine, and seminars at the American Association of Laboratory Animal Science (AALAS), Public Responsibility in Medicine and Research (PRIM&R), and Applied Research Ethics National Association (ARENA). They also met twice with occupational health physicians and with occupational health nurses. Key sections of the report will address zoonotic diseases transmissible from animals to humans; essential institutional policies, responsibilities, and authorities; allergies to animals; safety assessment; employees' serum banking and routine physical examinations; and recommendations for determining whether, for whom, and how often procedures should be performed. The report is being edited after which it will be reviewed by an independent NRC-appointed committee, and published by the National Academy Press in mid-1995. The committee roster is attached (see Appendix 1: ILAR Committee Rosters).

D. **Psychological Well-being of Nonhuman Primates.** The report responds to an amendment to the Animal Welfare Act, which requires institutions to develop programs to ensure the psychological well-being of nonhuman primates. It will provide readers with a

structure by which to develop a functional psychological well-being program; strategies for animal care personnel to use in developing enrichment techniques; strategies for animal care and use committees and veterinarians to use in assessing compliance with federal requirements; and strategies for animal welfare inspectors and site visitors to use in assessing the success of the program in achieving the goals of well-being. The report's recommendations will be even more valuable to the sponsors and users by virtue of the denial of a pending law suit to overturn current Animal Welfare Regulations and rewrite them as prescriptive, engineering standards. The committee's penultimate draft was edited and prepared for submission for review by an independent NRC-appointed committee and will be published by the National Academy Press in mid-1995. The committee roster is attached (see Appendix 1: ILAR Committee Rosters).

E. **Workshop on Biological Resource Databases.** On January 6-7, 1994, ILAR convened a workshop in which more than 50 experts in computer science; scientists who use biological resource databases; and representatives of federal agencies met to explore issues surrounding the rapid growth of biological databases and to discuss whether the NRC could help resolve problems associated with developing and maintaining biological resource databases and making them available to the scientific community cost-effectively. Five issues were discussed in detail: database integration, accessibility, quality control, intellectual property rights, and custodianship. Serious issues and needs were seen to exist in all areas, and the consensus of the group was that the NRC should conduct a study to address these issues.

Consequently, ILAR, in conjunction with the Board on Biology and in consultation with the Computer Science and Telecommunications Board and other appropriate NRC units, is planning to establish a committee of approximately 18 experts from pertinent areas of biological research (e.g., genetics, structural biology, developmental biology, systematics, and ecology), computer sciences and management. The committee will include experts in the development and implementation of community databases and users of the information contained in them. The committee will address the following issues:

- What databases currently exist, who needs access to databases, and what kinds of information are needed?
- How should a national information infrastructure for biological research be structured and how should it function?
- How should the national information infrastructure for biological research be implemented, funded, and managed?

The committee will hold a national workshop during 1995. The workshop will explore key issues for a national information infrastructure for biological research, especially what kinds of biological information are essential for such an infrastructure and alternative ways the infrastructure might be developed. There will be two reports published. The first will be the proceedings of the workshop, which is expected to stimulate further discussion in the scientific

community and to encourage additional input to the committee from the biological research community and others involved in the development of the infrastructure. The second will be the committee report, which will contain recommendations in the areas discussed above. Both reports will be subject to the NRC review process. The final committee report will include review by scientists and other appropriate experts in a broad range of disciplines. Dissemination of the report will include briefings for Congress, federal agencies, and others; articles in scientific journals; and presentations at professional society meetings.

F. **Workshop Series on Access to Biologicals for Research and Education.** Rules and regulations governing the collection, importation, and movement of biological materials across state and international boundaries have become increasingly complex and time consuming. Achieving compliance has become a serious concern for both investigators in a variety of scientific disciplines and for agency personnel who administer the regulations.

Understanding and complying with these laws, guidelines, and constraints is difficult, time consuming, and costly. Research institutions lack the specific information required to change the regulations or improve their compliance with them. Investigators are only generally informed about the regulations, and the majority of the public is totally unaware of them. Regulating agencies recognize the cost and difficulty of compliance but have limited resources by which to improve the permitting process.

To discuss whether an NRC study could assist with these problems, ILAR conducted a

workshop on March 16-17, 1994. This workshop was attended by scientists and administrators concerned with *obtaining* permits and scientists and administrators concerned with *granting* permits. There were presentations from the representatives of the pharmaceutical industry, field biologists, and representatives of agencies concerned with permitting.

Participants concluded that further workshops should be conducted by ILAR to assist in understanding and simplifying the permitting process. In October, 1994 a planning workshop was held and the content of the first three workshops was chosen to be:

- *Categorization and harmonization of information resources*. The types of import/export documents used by various agencies to administer the regulations should be cataloged and the terms used defined and harmonized. This would lead to a resource handbook (and possibly an electronic database) which could be used by both those applying for permits and by other agencies. [Specific case studies will be used to guide discussions.] Also, a review was requested of the balance between risk assessment and risk avoidance and the resulting regulations in light of Executive Order 12866 which calls for the use of performance standards by all agencies.
- *Impact of the permitting process*. Review is needed of the permitting process as it impacts on biodiversity research including planned, opportunistic, and existing collections and field research. This workshop would cover live and dead plants and animals, pests and their biocontrols, biological material, taxonomical identification, and

transport issues.

- *Biomedical and Toxicological issues.* This workshop would also apply to live and dead plants and animals; biological materials such as sera, cell lines, DNA, microorganisms; and taxonomical identification.

Future workshops would consider transport, import/export rules, international laws and regulations, packaging and shipping requirements; GATT, NAFTA, EC, Eastern Europe, Pacific Rim, and South American trade issues; and alternatives to the current permitting process and future strategies for working with agencies to simplify the process.

An NRC appointed steering committee, composed of members of ILAR Council, scientists, and science administrators with expertise in the specific workshop topic will, in conjunction with agency personnel and scientists, set the agenda and determine participants for each workshop. The steering committee will attend all workshops and will be responsible for preparation of the proceedings of each workshop. Four permitting agencies will likely participate in each workshop (e.g., Animal and Plant Health Inspection Service (APHIS) of the U.S. Department of Agriculture, National Marine Fisheries Service (NMFS) of the National Oceanographic and Atmospheric Administration, Fish and Wildlife Service (FWS) of the Department of Interior, and the Centers for Disease Control and Prevention (CDC) of the Department of Health and Human Services). Participants from other agencies will participate according to the agenda (e.g., Department of Transportation, Customs, Food and Drug Administration, Bureau of Land

Management, and the National Park Service). For some export activities the Department of Commerce grants permits and occasionally the Department of State is involved through their Agriculture Attaches or when treaties need to be negotiated. In addition other groups that could be involved included the National Science Foundation which has an international component and helps investigators obtain permits; Office of Science and Technology Policy at the White House, which has some interests in permitting; and NIH's Biosafety Office, which grants permits for CDC and obtains permits from APHIS.

It is precisely because responsibility for the regulation of the collection and movement of biologicals is vested so widely that this has become a complex and costly issue that needs to be addressed. In addition to agency representatives, participants representing societies will be selected from Association of Zoos and Aquaria, Association of Systematics and Collections, and Smithsonian Institution. Scientists from pharmaceutical and animal health industries, field and marine biology, natural history museums, botanists, and state biological surveys will also participate.

A series of workshops over three years is being planned. The short-range goal of each workshop is to enable dialogue between agency personnel and those affected by existing rules and policies. Summaries of each workshop will be published and members of various scientific societies will be encouraged to write articles to their various newsletters and journals to facilitate in the education of those readers. The long-range goal is to harmonize policies, facilitate their use, and enhance training of those who use these policies.

G. **A Workshop to Examine the Appropriate Use of Animals and Their Alternatives in Education.** This study is being proposed as a three-day workshop during which invited science teachers and administrators, biologists, veterinarians, and others will define the objectives of animal use, examine proper treatment of animals by students and teachers. Two reports will be developed by NRC-appointed steering committee. The first report will be a technical document that will reflect the workshop's discussions. The second will be a summary document for lay audiences, written by a popular science writer. The two reports will be of interest to teachers at the K-12 levels; school administrators; science coordinators; local, state, and federal officials; parents; and professional societies. Funding is being sought for this project. The office of Scientific Education, NIH, has agreed to take agency leadership for funding. The National Science Foundation has also expressed an interest, as have pharmaceutical companies.

H. **Transgenic Animals: Benefits and Risks.** Plans for a study of *Transgenic Animals: Benefits and Risks* were further elaborated in 1994. A workshop, led by the Commission on Life Sciences, is planned for 1995. The goal of this workshop is to explore the ethical and public policy issues involved in the development and use of biologically modified organisms. A science writer will participate in the workshop and assist in developing an informative booklet describing the risks and benefits of transgenic technology. The audience of the report is intended to be the public and Congress.

I. **The Cost of Research.** Plans for a study of *The Cost of Research* were initiated in 1994. A workshop is planned to explore the true costs of biological research, including animal costs (actual and indirect), administrative costs (oversight committees, paper work, and regulatory requirements), Office of Management and Budget (OMB) Circular A-21 (which prohibits indirect costs for animal colonies), and other issues. The audience of the report will be regulatory agencies and scientists.

CONCLUSIONS AND FUTURE DIRECTIONS

- Three NRC-appointed committees consisting of 41 volunteer members met for a total of 26 days in executive session, held 3 public meetings, conducted 7 seminars at national meetings, and met with 6 consultants.
- Two NRC-appointed committees consisting of 17 volunteer members finalized their reports. [*Dogs* was published and *Rodents* is in press.]
- A workshop on *Biological Resource Database's* was held. Thirty-eight invited participants met for two days resulting in recommendations for additional ILAR study.
- A workshop on *Collection and Importation of Biological Material, Animals, and Plants* was held. Forty-nine invited scientists and agency representatives met for two days resulting in recommendations for additional ILAR study.
- Three issues of *ILAR News* were published.
- *Dogs: Laboratory Animal Management Series* was published by the National Academy

Press.

- Four committee projects were continued in 1994, all of which are nearing completion for publication in mid-1995: *Occupational Health and Safety in the Care and Use of Research Animals*; *Psychological Well-being of Nonhuman Primates*; *Rodents: Laboratory Animal Management Series*; and revision of the *Guide for the Care and Use of Laboratory Animals*.

- Studies of *The Appropriate Use of Animals and Their Alternatives in Education*; *Transgenic Animals: Benefits and Risks*; and *The Cost of Research* were elaborated upon for initiation in 1995.

- *Laboratory Animal Management Documents* on *Ruminants*, *Swine*, and *Nonhuman Primates* were planned and fund raising undertaken.

- *ILAR News* will become *ILAR Journal* with the first issue of 1995. The new *ILAR Journal* will continue and expand the tradition of presenting thoughtful and timely scientific articles, commentary, and discussions on issues that impact the laboratory animal science community.

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Institute of Laboratory Animal Resources
National Research Council
Grant Number DAMD17-93-J-3016

Appendix 1
ILAR Committee Rosters

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Appendix 2
ILAR Reports

Dogs: Laboratory Animal Management Series
ILAR News, Volume 36, Number 1, Winter 1994
ILAR News, Volume 36, Number 2, Spring 1994
ILAR News, Volume 36, Number 3, Summer 1994 (Table of Contents)

INSTITUTE OF LABORATORY ANIMAL RESOURCES

Volume 36, Number 1 Winter 1994 National Research Council

Farm Animals in Biomedical Research—Part One

Swine in Biomedical Research: Management and Models

Transgenic Farm Animals

Issues for Institutional Animal Care and Use Committees (IACUCs)

Oversight of the Use of Agricultural Animals in University Teaching and Research

A quarterly publication for biomedical investigators, laboratory animal scientists, institutional officials for research, and members of animal care and use committees.

The Institute of Laboratory Animal Resources (ILAR) was founded in 1952 under the auspices of the National Research Council, which serves as an independent adviser to the federal government on scientific and technical questions of national importance. Jointly administered by the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine, the National Research Council brings the resources of the entire scientific and technical community to bear on national problems through its volunteer advisory committees.

ILAR is a component of the Commission on Life Sciences. Among its goals are to develop and make available scientific and technical information on laboratory animals and other biologic research resources to the federal government, the laboratory animal science and biomedical research communities, and the public. Guidelines developed by ILAR form a foundation for institutional and governmental policies on animal care and use.

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ILAR NEWS

INSTITUTE OF LABORATORY ANIMAL RESOURCES

VOLUME 36, NUMBER 1 WINTER 1994

CONTENTS

Swine in Biomedical Research: Management and Models

M. Michael Swindle, Alison C. Smith, Kathy Laber-Laird, and Laurel Dungan

INTRODUCTION

For the last 2 decades, swine have been used with increasing frequency in biomedical research as replacements for dogs and primates, as well as models of human disease based upon their own unique anatomy and physiology (Stanton and Mersmann, 1986; Swindle, 1992; Tumbleson, 1986).

All of the domestic farm breeds and miniature breeds available in the United States are *Sus scrofa domestica.* Farm breeds have the disadvantage of a rapid growth rate, increasing from an average weight of 1 kg at birth to 100 kg at 4 months of age. Mature breeding stock typically reach weights of greater than 200 kg. Consequently, these animals are best used for non-survival or short-term projects of less than 3 weeks in duration.

Miniature pigs are more commonly used for long-term projects because of their smaller size and growth rate. Depending on the breed, miniature pigs grow from a birth weight of 0.5 kg to 12-45 kg. at 4 months of age. Breeding stock reach weights of 45-100 kg. Commercially available miniature pigs also tend to be more tractable than domestic breeds raised in an agricultural setting. The most commonly used laboratory breeds of miniature pigs are Yucatan miniature, Yucatan Micropig®, Hanford, Sinclair (Hormel), Pitman-Moore, and Goettingen (Panepinto, 1986).

The purpose of this article is to review the use of swine in biomedical research and to provide general information on the husbandry and management of the various breeds in a laboratory setting. If an institution seeks to raise swine in large numbers, it would be well advised to consult an agricultural scientist involved in swine production programs for advice on facility design and management.

BIOMEDICAL MODELS

Swine are commonly used in cardiovascular research because swine and humans share important anatomic and physiologic characteristics. Their hearts are approximately the same size, and coronary blood flow, hemodynamic and myocardial contractility, development of atherosclerosis are analogous (Stanton and Mersmann, 1986). Consequently, swine are used to study congenital heart disease (Gillette et al., 1991; Mitchell et al., 1994; Swindle et al., 1992), myocardial infarction (Bloor et al., 1992), hemodynamics and shock (Hannon, 1992; Hoban et al., 1992), development of interventional radiology devices including balloon catheters and intravascular stents (Gal and Isner, 1992; White et al., 1992), hypertension (Zambraski et al., 1992), cardiopulmonary bypass and anesthesia (Cameron et al., 1992; Weiskopf et al., 1992), heart failure (Hendrick et al., 1990), and atherosclerosis (Lee et al., 1986).

Swine are also used extensively for nutritional studies because their digestive physiology is similar to humans. Because they are omnivores, swine will readily consume a variety of nutritional supplements and test substances (Swindle et al., 1988). They have also been used for many other studies related to nutrition, including total parenteral nutrition, lipid metabolism, diabetes, alcoholism, gastric ulceration, and splanchnic blood flow (Cohen et al., 1992; Laber-Laird et al., 1992; Tumbleson, 1986).

Organ transplantation studies have been performed using the swine heart (Hall et al., 1986), liver (Flye, 1992), kidney (Pennington, 1992), pancreas (Koyama et al., 1986), and intestine (Pritchard et al., 1986). Many of these organ transplantation studies have been related to immunologic aspects of transplants, including the development of transgenic animals that would be immunologically accepted by humans (Sachs, 1992).

Other studies have involved wound healing and plastic and reconstructive surgery (Kerrigan et al., 1986), fetal surgery (Randall, 1986), and pharmacology and toxicology (Kurihara-Bergstrom et al., 1986; Feletou and Teisseire, 1992). Reproductive physiology and endocrine functions have also been studied (Tumbleson, 1986).

Swine are used extensively in surgical training classes for health care practitioners. Initially they were used to train medical students and residents in surgical skills (Swindle and Bobbie, 1983) but are now used extensively to train graduate physicians, nurses, and technical staff in endoscopic and stapling surgical techniques, laser surgery, and microsurgery.

When comparing studies using swine, the differences in physiology, genotype, and phenotype and in maturity at a

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given body weight need to be considered, not only among breeds, but among breeds from different producers. It is best to use the same breed and age, however, this is not always possible. In order to make hemodynamic comparisons, values should be indexed to body weight in kilograms or body surface area. Because of varying growth rates among breeds, animals may differ in age and maturity at the same weight. This factor should also be considered when comparing data (Smith et al., 1990; Smith et al., in press). Genotype matching has become increasingly important in achieving reproducibility among animals.

Anesthesia, analgesia, and surgical care are important subjects and have received much attention in the literature. Reviews on these important subjects are available (Riebold and Thurmon, 1986; Smith et al., in press; Swindle et al., 1988).

HUSBANDRY

Guidelines for housing laboratory swine have been published in the *Guide for the Care and Use of Laboratory Animals* (*Guide*) (NRC, 1985) and in the *Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching* (*Ag Guide*) (Consortium for Developing a Guide, 1988), which require that swine be housed in facilities comparable to a well-managed farm. Also, the proceedings of a Scientists Center for Animal Welfare conference provide recommendations for husbandry and handling of swine (Mench et al., 1992). Although agricultural animals, including swine, are now covered by the Animal Welfare Act and consequently are regulated by the U.S. Department of Agriculture, no written standards are available to date. While the guidelines listed above do not take miniature pigs into consideration, a comparison of husbandry practices for miniature pigs with those of domestic farm breeds has recently been published (Fisher, 1993).

The recommendations in both the *Guide* and the *Ag Guide* for housing and grouping swine are confusing and contradictory and neither takes miniature pigs into consideration. The *Guide* has more stringent requirements for floor space than the *Ag Guide* and should be used as the standard for biomedical institutions. The *Guide* requires 6 to 60 square feet per pig (0.56–5.57 sq m/pig) depending upon the body weight and the number of animals housed within the same enclosure. It does not distinguish between a sow with a litter and groupings of more mature animals. The *Ag Guide* recommends 35 sq ft (3.15 sq m) for a sow with a litter. In our experience, miniature pigs with litters actually require less space than could be calculated from the standards in either document. A variance of this type should be reviewed by the institution's IACUC.

Ambient temperature requirements for swine are not listed in the *Guide*, but the *Ag Guide* recommends a temperature range of 50°–77°F (10°–25°C) for adult animals and temperature ranges of 59°–90° (15°–32°C) for less mature animals with the higher values being required for neonates. Based on our experience with miniature swine, temperatures should be between 75°–80°F (24°–26°C). Heat lamps or other heat sources should be placed in the corner of the cage to provide extra warmth for neonates, which typically require temperatures of 85°–90°F (30°–32°C). Care must be taken to ensure that temperature measurements are made at the level of the animals because of the differential between the floor and wall thermostats (Fisher, 1993). Care should also be taken to ensure that animals are kept dry while the pens are being cleaned, as wet animals frequently become chilled. Animals housed in agricultural situations can withstand a wide range of temperatures if shelter is available.

Humidity and air changes are not detailed by existing guidelines. We use rooms with 10-15 air changes per hour with 100 percent fresh outside air and a relative humidity of 40–70 percent, which is consistent with general American Association for Accreditation of Laboratory Animal Care (AAALAC) facility standards. If lighting is provided by artificial means with light timers, the lighted cycle should be 12–16 hours especially if breeding is performed (Consortium for Developing a Guide, 1988; Fisher, 1993).

Swine are best housed in pens made of chain link or panels with vertical slats or bars. If solid floors are used, they should be deeply bedded with wood shavings to prevent the animals from slipping. The wood shavings also provide environmental enrichment as they are a substance in which the pigs can root. Extra care must be taken when using wood shavings with animals that are being fasted before surgery, as they will eat the bedding. Raised slotted flooring or slatted floors are also acceptable as long as a type with small openings is used to prevent hoof injury (Figure 1). If animals are housed on raised floors, a regular program of hoof trimming will have to be provided for long-term animals (those held for more than 3 months). Dog cages provide good short-term housing for special purposes such as postoperative care, however, either raised floors or non-skid pads need to be placed in the cages.

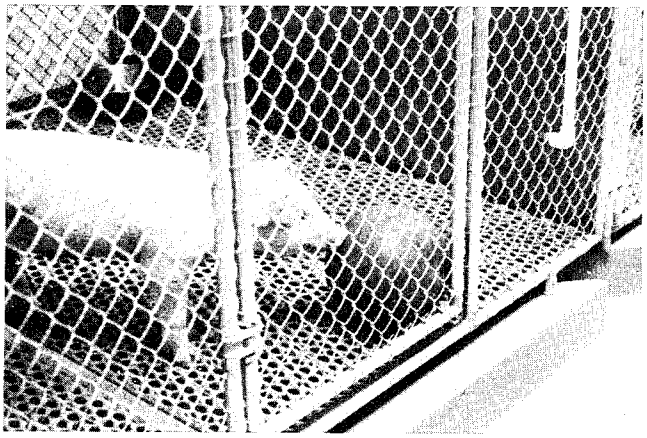

FIGURE 1 Pig housed in a chain length run on raised flooring. Note the use of automatic watering and the presence of a teflon ball for environmental enrichment.

Facilities that maintain breeding swine need to provide for farrowing and weaning. Domestic farm breeds, but not miniature breeds, require a farrowing crate or pen to prevent them from crushing the piglets. If the piglets are allowed access to heat lamps and bedding for warmth, it is our experience that farrowing crates or even separation panels are unnecessary. Piglets will start to consume feed at approximately 3 weeks, and the starter ration should be provided in an area of the pen not accessible by the sow. Domestic farm breeds have an average gestation period of 114 days, while some of the miniature breeds farrow at shorter times (for example, the Yucatan pig has a gestation period of 111 days). Weaning for both domestic and miniature breeds occurs at 3 to 6 weeks.

Swine are social animals and should be provided with the opportunity to interact with other members of their species and with humans. If housing by compatible groups is not possible because of protocol restrictions or cage size, then animals should be able to see each other and preferably touch noses through the walls of the pens. Incompatible animals will fight and dominant animals may severely injure others in the pen especially at feeding time. If animals are housed without bedding, then toys such as basketballs or large balls made of impervious materials can be provided to satisfy the rooting behavior. Swine can be trained and made docile by positive interactions with humans such as rubbing or scratching the head and back. Animals may also be trained with food rewards of vegetables or fruit. Stressful housing situations in combination with other factors, including diet and environmental fluctuations, may result in gastric ulceration (Panepinto, 1986; Swindle et al., 1988).

In biomedical research institutions, standard formulations of commercial agricultural feed should be avoided. Commercial farm rations are designed to provide rapid growth and contain antibiotics and other growth promoters unless special formulations are requested. Several commercial manufacturers now provide diets for miniature pigs which are higher in fiber and provide for less rapid growth without compromising nutritional requirements. Starter, maintenance, and lactation diets are available and a calculated amount may be fed either once or twice a day. Pigs will readily consume medications mixed in normal rations or camouflaged with either canned dog food or chocolate syrup. Pigs will form a dunging pattern and will usually defecate opposite from where their food is provided depending upon the cage configuration. More information on nutrient requirements for swine can be found in NRC (1988).

Water is best provided by an automated watering system as water deprivation can easily occur because pigs will refuse to drink from soiled water containers and quickly overturn floor pans and water bowls. Care must be taken not to deprive them of water for long periods of time, even preoperatively, because they are susceptible to "salt poisoning." This condition results in clinical neurologic deficits secondary to water deprivation or over-administration of sodium salts in as little as 12 hours (Fisher, 1993).

HANDLING

Restraint methods, commonly used in agricultural settings such as "snout snaring" or other aggressive physical types of restraints should be discouraged in biomedical research institutions because of the stress they induce. Swine may be humanely restrained in commercially available restraint slings (Figure 2) or institutions may construct their own (Panepinto, 1986). Swine may be herded into the corner of a pen using a handheld plywood or plastic panel when restraint is necessary in the pen. If restrained manually, they should be held in the same manner as dogs and not held upside down by the rear legs. Physical examinations, rectal temperature checks, and injections may be performed while a pig is distracted by food.

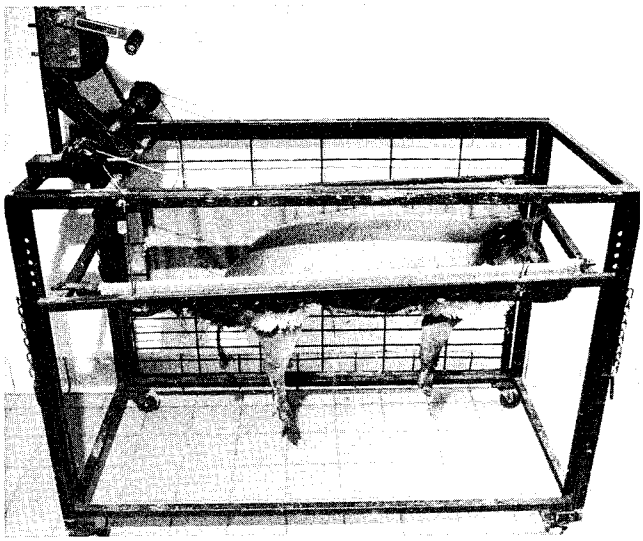

FIGURE 2 Yucatan miniature pig humanely restrained in a Panepinto sling.

Short-term chemical restraint agents and anesthetics may be used if the procedure requires them. Techniques and agents are reviewed elsewhere (Riebold and Thurmon, 1986; Smith et al., in press; Swindle et al., 1988).

HEALTH CARE

The best method to ensure having healthy research animals is to procure them from a reliable source, which has been evaluated by the institutional veterinarian. The health status of domestic farm breeds is variable depending upon the endemic diseases in the region of the country and the quality of the management and health care program of the farmer. Purchasing pigs at auctions is almost certain to introduce porcine diseases to the research facility. Specific-pathogen free (SPF) status is a specific term in swine management ensuring that the source of animals is free of many infectious and parasitic diseases with a notable exception being myco-

plasmosis. While non-SPF sources may still be healthy and suitable for research, the animals should be evaluated by a veterinarian. Regardless of the source of the animals, our experience is that a 3-day stabilization period following shipment is recommended for animals undergoing survival surgical procedures. Depending on the source of the animal, quarantine and conditioning programs may be necessary for animals on long-term projects. If research animals are being maintained for long-term projects, it may be necessary to establish a vaccination program. Potential pathogens to vaccinate for include Bordetella, Pasteurella, erysipelas, Hemophilus, Clostridium, parvovirus, leptospira, Escherichia coli, transmissible gastroenteritis, and rotavirus. Veterinary advice should be sought on which organisms are of particular importance to the research facility. A program to control internal and external parasites should also be established based on a physical examination and an evaluation of fecal samples.

If a facility is raising neonates, a program of care should include clipping the needle teeth and injecting iron dextran to protect against physiologic anemia, which occurs in newborn pigs.

Health programs for miniature swine are the same as for domestic farm breeds, and in-depth discussions of health management programs are available in veterinary textbooks (Leman et al., 1992).

SUMMARY

Swine, both miniature and domestic farm breeds, will continue to be used in research and teaching in the foreseeable future. Biomedical models have been well described (Stanton and Mersmann, 1986; Swindle, 1992; Tumbleson, 1986) and overviews of methods of anesthesia, analgesia, and handling appropriate for research institutions are available (Riebold and Thurmon, 1986; Smith et al., in press; Swindle et al., 1988). The differences between miniature pigs and domestic farm breeds, as well as the differences among breeds within the same category, must be taken into account when designing scientific protocols and management plans.

This manuscript is meant to provide general guidelines for multi-species research institutions that may only occasionally use swine. Readers are advised to consult the in-depth references provided for specific details.

REFERENCES

Bloor, C. M., F. C. White, and D. M. Roth. 1992. The pig as a model of myocardial ischemia and gradual coronary artery occlusion. Pp. 163-175 in Swine as Models in Biomedical Research, M. M. Swindle, ed. Ames, Iowa: Iowa State University Press.

Cameron, D. E., K. H. Tam, W. Cheng, and M. Braxton. 1992. Studies in the physiology of cardiopulmonary bypass using a swine model. Pp. 185-196 in Swine as Models of Biomedical Research, M. M. Swindle, ed. Ames, Iowa: Iowa State University Press.

Cohen, I. T., S. O. Nelson, and M. P. Hirsh. 1992. The role of the Hanford minipig as an animal model in pediatric surgery and neonatal intensive care. Pp. 57-63 in Swine as Models in Biomedical Research, M. M. Swindle, ed. Ames, Iowa: Iowa State University Press.

Consortium for Developing a Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching. 1988. Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching. Champaign, Illinois: Association Headquarters (Available at a cost of $5.00 each from Association Headquarters, 309 West Clark Street, Champaign, IL 61820. Tel: 1-217-356-3182).

Feletou, M., and B. Teisseire. 1992. Vascular pharmacology of the micropig: Importance of the endothelium. Pp. 74-95 in Swine as Models in Biomedical Research, M. M. Swindle, ed. Ames, Iowa: Iowa State University Press.

Fisher, T. F. 1993. Miniature swine in biomedical research: Applications and husbandry considerations. Lab Animal 22(5):47-50.

Flye, M. W. 1992. Orthotopic liver transplantation in outbred and partially inbred swine. Pp. 44-56 in Swine as Models in Biomedical Research, M. M. Swindle, ed. Ames, Iowa: Iowa State University Press.

Gal, D., and J. M. Isner. 1992. Atherosclerotic Yucatan microswine as a model for novel cardiovascular interventions and imaging. Pp. 118-140 in Swine as Models in Biomedical Research, M. M. Swindle, ed. Ames, Iowa: Iowa State University Press.

Gillette, P. C., M. M. Swindle, R. P. Thompson, and C. L. Case. 1991. Transvenous cryoablation of the bundle of His. PACE 14(4) Pt1:504-510.

Hall, T. S., R. S. Stuart, W. A. Baumgarten, A. M. Borkon, M. M. Swindle, E. Galloway, and B. A. Reitz. 1986. Use of swine in heart transplantation research. Pp. 373-76 in Swine in Biomedical Research, M. E. Tumbleson, ed. New York: Plenum Press.

Hannon, J. P. 1992. Hemorrhage and hemorrhagic shock in swine. A review. Pp. 197-245 in Swine as Models in Biomedical Research, M. M. Swindle, ed. Ames, Iowa: Iowa State University Press.

Hendrick, D. A., A. C. Smith, J. M. Kratz, F. A. Crawford, and F. G Spinale. 1990. The pig as a model of tachycardia and dilated cardiomyopathy. Lab Anim. Sci. 40(5):495-501.

Hoban, L. D., J. A. Paschall, J. Echsktein, V. Nadkarni, R. L. Che-Hung, T. J. Williams, D. Rensch, J. J. Nevola, and J. A. Carcillo. 1992. Awake porcine model of intraperitoneal sepsis. Pp. 246-264 in Swine as Models in Biomedical Research, M. M. Swindle, ed. Ames, Iowa: Iowa State University Press.

Kerrigan, C. L., R. G. Zelt, J. G Thornsom, and E. Diane. 1986. The pig as an experimental animal in plastic surgery research for the study of skin flaps, myocutaneous flaps and fasciocutaneous flaps. Lab Anim. Sci. 36:396.

Koyama, I., L. R. Pennington, M. M. Swindle, and G. M. Williams. 1986. Pancreatic allotransplantation with Roux-en-Y jejunal diversion in swine: Its technical aspects. Pp. 385-89 in Swine in Biomedical Research, M. E. Tumbleson, ed. New York: Plenum Press.

Kurihara-Bergstrom, T., M. Woodworth, S. Feisullia, and P. Beall. 1986. Characterization of the Yucatan miniature pig skin and small intestine for pharmaceutical applications. Lab Anim. Sci. 36:396.

Laber-Laird, K., A. C. Smith, M. M. Swindle, and J. Colwell. 1992. Effects of isoflurane anesthesia on glucose clearance in Yucatan minipigs. Lab Anim. Sci. 42(6):579-581.

Lee, K. T., D. N. Kim, and W. A. Thomas. 1986. Atherosclerosis in swine. Pp. 33-48 in Swine in Cardiovascular Research, Vol. 1, H. C. Stanton and H. J. Mersmann, eds. Boca Raton, Fla.: CRC Press.

Leman, A. D., B. E. Straw, W. L. Mengeling, S. D'Allaire, and D. J. Taylor. 1992. Diseases of Swine, Seventh Edition. Ames, Iowa: Iowa State University Press.

Mench, J. A., S. J. Mayer, and L. Krulisch, eds. 1992. The Well Being of Agricultural Animals in Biomedical and Agricultural Research. Bethesda, Maryland: Scientists Center for Animal Welfare.

Mitchell, S. E., J. H. Anderson, M. M. Swindle, J. D. Strandberg, and J. Kan. 1994. Atrial septostomy: Stationary angioplasty balloon technique. Experimental work and preliminary clinical applications. Pediatr. Cardiol. 15(1):1-7.

NRC (National Research Council). 1985. *Guide for the Care and Use of Laboratory Animals*. A report of the Institute of Laboratory Animal Resources Committee on Care and Use of Laboratory Animals. Washington, D.C.: U.S. Department of Health and Human Services.

Panepinto, L. M. 1986. Character and management of miniature swine. Pp. 11-24 in Swine in Cardiovascular Research, Vol. 1, H. C. Stanton and J. H. Mersmann, eds. Ames, Iowa: Iowa State University Press.

Pennington, L. R. 1992. Renal transplantation in swine. Pp. 35-43 in Swine as Models in Biomedical Research, M. M. Swindle, ed. Ames, Iowa: Iowa State University Press.

Pritchard, T. J., W. A. Kottun, and R. L. Kirkman. 1986. Technical aspects of small intestinal transplantation in young pigs. Pp. 391-398 in Swine in Biomedical Research, Vol. 1, M. E. Tumbleson, ed. New York: Plenum Press.

Randall, G. C. B. 1986. Chronic implantations of catheters and other surgical techniques in fetal pigs. Pp. 1179-1186 in Swine in Biomedical Research, Vol. 1, M. E. Tumbleson, ed. New York: Plenum Press.

Riebold, T. W., and J. C. Thurmon. 1986. Anesthesia in Swine. Pp. 243-254 in Swine in Biomedical Research, Vol. 1, M. E. Tumbleson, ed. New York: Plenum Press.

Sachs, D. H. 1992. MHC-homozygous miniature swine. Pp. 3-15 in Swine as Models in Biomedical Research, M. M. Swindle, ed. Ames, Iowa: Iowa State University Press.

Smith, A. C., F. G. Spinale, and M. M. Swindle. 1990. Cardiac function and morphology of Hanford miniature swine and Yucatan miniature and micro swine. Lab Anim. Sci. 40(1):47-50.

Smith, A. C. W. Ehler, and M. M. Swindle. In press. Anesthesia and analgesia in swine. In Anesthesia and Analgesia in Laboratory Animals. D. H. Kohn, S. K. Wixson, W. J. White, and G. J. Benson, eds. New York: Academic Press.

Stanton, H. C., and Mersmann, H. J. 1986. Swine in Cardiovascular Research, Vol. 1 and 2. Boca Raton, Florida: CRC Press.

Swindle, M. M., ed. 1992. Swine as Models in Biomedical Research. Ames, Iowa: Iowa State University Press.

Swindle, M. M., and D. L. Bobbie (illustrator). 1983. Basic Surgical Exercises Using Swine. New York: Praeger Publishers.

Swindle, M. M., A. C. Smith, and B. J. S. Hepburn. 1988. Swine as models in experimental surgery. J. Invest. Surg. 1(1):65-79.

Swindle, M. M., R. P. Thompson, B. A. Carabello, A. C. Smith, C. Green, and P. C. Gillette. 1992. Congenital cardiovascular disease. Pp. 176-184 in Swine as Models in Biomedical Research, M. M. Swindle, ed. Ames, Iowa: Iowa State University Press.

Tumbleson, M. E., ed. 1986. Swine in Biomedical Research, Vol. 1, New York: Plenum Press.

Weiskopf, R. B., M. A. Holmes, E. I. Eger II, N. Yasuda, I. J. Rampil, B. H. Johnson, A. G. Targ, I. A. Reid, and L. C. Keil. 1992. Use of swine in the study of anesthetics. Pp. 96-117 in Swine as Models in Biomedical Research, M. M. Swindle, ed. Ames, Iowa: Iowa State University Press.

White, C. J., S. R. Ramee, A. K. Banks, D. Wiktor, and H. L. Price. 1992. The Yucatan miniature swine: An atherogenic model to assess the early potency rates of an endovascular stent. Pp. 156-162 in Swine as Models in Biomedical Research, M. M. Swindle, ed. Ames, Iowa: Iowa State University Press.

Zambraski, E. J., G. D. Thomas, and K. P. O'Hagan. 1992. DOCA-treated Yucatan miniature swine: A neurogenic model of essential hypertension. Pp. 290-301 in Swine as Models in Biomedical Research, M. M. Swindle, ed. Ames, Iowa: Iowa State University Press.

Transgenic Farm Animals

Caird E. Rexroad, Jr.

INTRODUCTION

The insertion of new genetic material, frequently recombinant genes, into the genome of animals to produce "transgenic" animals is a powerful method to determine how genes program the development, growth, maturation, and senescence of animals. Improved understanding of genetic regulation offers the potential to make rapid improvements in production of food and fiber. Transgenic farm animals may also produce novel products such as pharmaceuticals. Farm animals have long been used as model systems in human health studies. Transgenic farm animal models for some diseases will provide better models than genetically modified mice and rats. Sheep, pigs, rabbits (Hammer et al., 1985), cows (Biery et al., 1988; Roschlau et al., 1989), goats (Denman et al., 1991), farmed fish (trout: Chourrout et al., 1986; catfish: Dunham et al., 1987), and chickens (Salter et al., 1986) have been genetically modified. This report will focus on the progress that has been made in the production of potentially useful large transgenic farm animals.

ANIMAL PRODUCTIVITY

Remarkable growth in growth hormone (GH) transgenic mice (Palmiter et al., 1982) led to experiments to produce transgenic pigs and sheep to study how to genetically modify livestock to improve growth and body composition. These animals carry fusion transgenes consisting of the mouse metallothionein-I promoter ligated to the structural gene for human growth hormone (hGH) (Hammer et al., 1985). The fusion gene construct was designed to direct growth hormone production to tissues normally producing metallothionein-I thus removing growth hormone from its usual negative feedback loop. The same fusion gene had increased the growth rate and total body size of transgenic mice, and its effects could be induced by feeding zinc ions to "turn on"

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the promoter. Regulation of metallothionein-I:growth hormone fusion genes was different in sheep and pigs than in mice. In both sheep and pigs, the fusion genes increased basal GH concentrations in blood (Pursel et al., 1987; Rexroad et al., 1989, 1991), but induction with zinc ions was marginal in pigs (Pursel et al., 1989). Poor regulation was also observed in sheep when a sheep metallothionein promoter was fused to a sheep growth hormone structural gene; extremely high basal production of growth hormone resulted (Murray et al., 1989). Restriction of the mineral content in the diet of livestock may not be satisfactory for regulating the metallothionein promoter.

Untoward results from overexpression led to the use of other growth hormone constructs to modify the pattern of growth hormone secretion. Transgenic pigs were made that carried a transgene consisting of the phosphoenolpyruvate carboxykinase (PEPCK) promoter ligated to a GH gene. While the transgene in mice was sensitive to changing dietary energy level, growth hormone was expressed at unsatisfactorily high levels in transgenic pigs (Wieghart et al., 1990).

Another approach to modifying growth hormone production was to increase the endogenous output of growth hormone. Transgenic swine and sheep were produced with a metallothionein-I:human growth hormone releasing factor transgene (hGRF) (Pursel et al., 1989; Rexroad et al., 1989) or with an albumen:hGRH transgene (Rexroad et al., 1991). This approach increased the circulating concentration of growth hormone in lambs but not in swine. In hGRF transgenic sheep, the concentration of growth hormone, while lower than in growth hormone transgenic lambs, was high and led to metabolic abnormalities. In pigs, peripheral production of human growth hormone releasing factor did not alter growth hormone secretion because a circulating dipeptide peptidase inactivated the hGRF.

Overproduction of growth hormone increased the growth rate of pigs and reduced the amount of feed required per unit of weight gain (Pursel et al., 1989). The most positive aspect from the production point of view was that growth hormone transgenic pigs had greatly reduced body fat. Excess growth hormone production had several negative effects, including lack of sexual drive in both males and females and joint problems (Pursel et al., 1989). Overproduction of growth hormone in sheep resulted in elevated plasma and urinary glucose after 100 days of age and reduced circulatory insulin (Rexroad et al., 1991). Sheep with overexpression also had renal degeneration (Nancarrow et al., 1991). The results of overexpression appear to be similar whether the expressed gene is from the same or a different species in both pigs and sheep.

Overexpression of growth hormone consistently resulted in very lean sheep that were diabetic (Murray et al., 1989; Nancarrow et al., 1991; Rexroad et al., 1989, 1991). Overexpression of growth hormone in pigs resulted in some consistent features such as leanness and anestrus. Traits such as improved growth efficiency and reduced feed consumption varied to about the same degree as controls. Some negative phenotypes such as gastric ulcers were highly variable and may have depended on the genetic background of the original transgenics.

These studies in pigs and sheep indicate that more sophisticated knowledge of the regulation of growth and the effects of various peptide effectors is needed in order to genetically modify livestock for growth and composition of growth in livestock. Such intervention also requires more subtle knowledge of the construction and insertion of transgenes. The transgenic approach will be useful for continued studies in this area, but the number of studies that can be completed is limited by the low efficiency of production of expressing transgenics by DNA microinjection. These studies also clearly indicate that while the mouse is a good model for gene expression, its usefulness may be limited by differences in physiological responses to gene products.

MILK MODIFICATION

An important source of protein production for growth and body composition is the dairy cow. In the U.S., cows produced about 2,170,000,000 kg of protein in milk in 1991 (Agricultural Statistics, 1992). The transgenic approach has been suggested as a means to improve the quality of milk protein for human consumption, especially for infants; to improve quality of dairy products, such as cheese; and as a source of peptide pharmaceuticals.

Research on modification of milk for nutritional value is in its infancy, but modification of milk for the production of proteins of pharmaceutical value is well underway. Two particular studies are of interest. A commercial academic consortium produced transgenic sheep with fusion transgenes consisting of the sheep beta lactoglobin promoter linked to either the human blood clotting factor IX structural gene (Clark et al., 1989) or to the α-1 antitrypsin (α1-AT) structural gene (Wright et al., 1991). In both cases milk was produced that contained the transgene product. In the case of α1AT, one founder ewe produced 50 percent of her milk protein as α1AT, which was N-glycosylated and biologically active. Human tissue plasminogen activator was produced in the milk of goats and was enzymatically active (Ebert et al., 1991). These results clearly indicate that transgenic farm animals have the potential to serve as self-perpetuating bioreactors, since offspring have been produced that carry the transgene.

Surprisingly, pigs have also been used to produce pharmaceuticals in their mammary glands. Protein C, a regulator of hemostasis, was produced by a group at Virginia Polytechnic Institute and State University in Blacksburg, Virginia. Although pigs are not traditionally used for milk production in animal agriculture, they are valuable animals for transgenic studies because of their litter size. The milk produced by transgenic pigs contained protein C, with anticoagulant activity, at up to 1 g/l (Velander et al., 1992). Technology is being developed for the machine milking of pigs.

While it might be expected that cows would be the main

focus of such research, the long generation interval from the microinjection of eggs until production of milk (nearly 3 years), suggests that most projects will await our ability to determine that microinjected cow embryos are carrying transgenes that are likely to function. Nonetheless, the ability to mature, fertilize, and culture cow embryos in vitro for the production of blastocysts has maintained transgenic research on cows, and at least one founder bull has been produced carrying the human lactoferrin gene (Krimpenfort et al., 1991)

OTHER HEALTH-RELATED ISSUES

Livestock species have long provided tissues or tissue extracts for treatment of human illness. Pig hearts, for example, have provided valves for transplantation. The transgenic approach has suggested several possibilities. Swanson et al. (1992) produced functional human hemoglobin in transgenic swine, although a number of factors limit its immediate usefulness. Whole organs from livestock that have been genetically modified so that the host immune response is not elicited, may be available for transplant to humans.

ANIMAL HEALTH

Protection of animals from disease may be one of the best applications for transgenes. The normal route of attack for pathogens on animals may rely on essentially a single genetic system. In mice and chickens, retroviral attacks may be reduced by the presence of a single gene product. Mice expressing the FV4 gene, which has a product similar to the MoLV viral envelope, are resistant to MoLV infection (Ikeda and Sugimura, 1980). Transgenic chickens carrying a defective avian leukosis virus contain only the gene for the envelope protein (Crittenden and Salter, 1990) and were resistant to infection and oncogenesis by wild type strains of virus.

A disease of sheep with serious economic consequence is ovine progressive pneumonia. This disease results from an attack on the immune system by the visna virus, a lentivirus related to the HIV retrovirus. In order to study the possibility of preventing infection by the overexpression of envelope protein in the target cell, we produced transgenic sheep carrying a transgene consisting of the visna LTR fused to the visna envelope protein. Three lambs were born that expressed the construct. The transgene is expressed in macrophages, the appropriate tissue; in culture, the secretion of the envelope protein causes cell fusion as expected. Unfortunately, all three lambs were female, and it will take some time to expand the populations to be able to test in vivo resistance to visna infection.

Transgenic technology may also aid in the prevention of neonatal diseases by the introduction of preformed antibodies. Lo et al. (1991) reported the generation of transgenic livestock using the mouse α and κ chain for antibodies against phosphorylcholine. Mouse IgA was present in serum in pigs, although an intact mouse κ transgene was not present, so presumably had pig light chains. In one sheep, IgA was present in peripheral lymphocytes but not in serum, and an intact mouse γ gene was not functional. Weidl et al., (1991) introduced Ig heavy and light chains from an IgG1 secreting hybridoma. The antibody was directed to 4-hydroxy-3-nitrophenylacetate. The genes were injected in a single vector. One transgenic pig had high serum titers of antibody, but only part of the reactive antibody was identical to purified mouse antibody. These first studies are interesting because they indicate the possibility of introducing preformed antibody genes without obvious suppression of endogenous antibody production.

METHODS OF PRODUCING TRANSGENES

Transgenic cows, pigs, sheep, and goats were produced by the microinjection of DNA into pronuclei of fertilized ova or into a nucleus of two-cell zygotes. Microinjection results in the insertion of a variable number of copies of the transgene into unspecifiable locations in the genome. Multiple copies are usually present at the same insertion site as an array. The process that incorporates microinjected DNA into the genome is not understood and results in low efficiency of production of useful transgenic farm animals. The overall production rate of cows, pigs, and sheep in several experiments was less than one percent of injected embryos (Rexroad, 1992). The 99 percent loss includes all those associated with embryo microinjection, culture, transfer, and failure to develop. The one percent of transgenics that are produced may have to undergo selection for usefulness. In farm animals, only about half of the transgenic offspring express the transgene. The percentage has varied widely from experiment to experiment and probably reflects, at the least, variation associated with the "strength" of the promoter and the site of insertion of the transgene into the genome. Expressing animals may vary in the level of expression as a result of variation in copy numbers. A further constraint is that many transgenics are mosaics, meaning they have two or more distinct cell lines, resulting either from a late integration event or a gene deletion event during development. Mosaicism has been estimated to be as high as 30 percent in mouse transgenics, and breeding studies in farm animals also suggest its presence (Wilkie et al., 1986). The proportion of embryos that incorporate a transgene is not known and is difficult to determine. Microinjected DNA persists in embryos throughout the period that they would be culturable in vitro, and thus it is difficult to determine when an integration event has occurred by most techniques.

Transgenic farm animals exist for over 50 different gene constructs. A wide variety of genes have been expressed in transgenics, including human, mouse, bovine, porcine, and ovine (Pursel et al., 1989; Rexroad, 1992). In addition, viral and bacterial genes have been expressed. A wide variety of promoters have been used, and tissue specificity has been

demonstrated for tissues such as the mammary gland. Transgenic farm animals may have great value as bioreactors to produce peptide pharmaceuticals at high levels with appropriate post-transcriptional modification.

FUTURE PROSPECTS

A number of recent findings may increase the efficiency of producing transgenic farm animals and give us the ability to make precise genetic modifications. Wall et al. (1992) reported that using chicken lysosomal matrix attachment regions (MARS) in mice improved the efficiency of producing mice that express the desired gene when the WAP (whey acidic protein) gene was coinjected with the MARS. These findings would impact farm animals in two ways if applicable. MARS or similar elements would be expected to confer more precise regulation and also ensure expression, which would increase the efficiency of producing transgenics that express the desired gene almost twofold for livestock species. A similar procedure was co-injection of an efficiently expressed gene (sheep β-lactoglobin) with otherwise poorly expressed genes. This "rescue" improved the expression of the co-injected gene (Clark et al., 1992). Co-incorporation into the genome may have provided an active minilocus. Another opportunity is of course the possibility of producing stem cells from livestock species that might be genetically engineered with precision. Sims and First (1993) reported the culture of inner cell mass-derived cells from cattle with their subsequent use as donors of nuclei in the production of cloned cattle. If such cells can be genetically modified, as are stem cells in mice, then the genetic modifications that can be attempted will be relatively unlimited, including insertion, deletion, and replacement of genes. Stem cells in livestock species offer some potential advantages over stem cells from mice. In livestock species, nuclear transfer can be accomplished with cells from the inner cell mass. If stem cells have the same potency as cells of the inner cell mass, then nuclear transfer rather than chimera formation might be used, thus reducing the number of generations needed to produce germ line transgenics.

Transgenic mice have drawn immense attention for their usefulness in studying gene expression and in understanding many disease states. Research on transgenic livestock is comparatively in its infancy. Transgenesis may improve animal health and the healthfulness of animal products. Transgenic livestock acting as bioreactors, tissue donors, and organ donors may have the potential to improve human health.

REFERENCES

Agricultural Statistics. 1992. Pp. 302-304. U.S. Department of Agriculture.

Biery, K. A., K. R. Bondioli, and F. J. De Mayo. 1988. Gene transfer by pronuclear injection in the bovine. Theriogenology 29:224. (Abstr.).

Chourrout, D., R. Guyomard, and L.M. Houdebine. 1986. High efficiency gene transfer in rainbow trout (Salmo gairdneri Rich.) by microinjection into egg cytoplasm. Aquaculture 51:143-150.

Clark, A. J., H. Bessos, J. O. Bishop, P. Brown, S. Harris, R. Lathe, M. McClenaghan, C. Prowse, J. P. Simons, C. B. A. Whitelaw, and I. Wilmut. 1989. Expression of human anti-hemophilic factor IX in the milk of sheep. Biotechnology 7:487-492.

Clark, A. J., A. Cowper, R. Wallace, G. Wright, and J. P. Simons. 1992. Rescuing transgene expression by co-integration. Bio/Technology 10:1450-1454.

Crittenden, L. B., and D. W. Salter. 1990. Expression of retroviral genes in transgenic chickens. J. Reprod. Fert. Suppl. 41:163-171.

Denman, J., M. Hayes, C. O'Day, T. Edmunds, C. Bartlett, S. Hirani, K. M. Ebert, K. Gordon, J. M. McPherson. 1991. Transgenic expression of a variant of human tissue-type plasminogen activator in goat milk: Purification and characterization of the recombinant enzyme. Bio/Technology 9:839-843.

Dunham, R. A., J. Eash, J. Askins, and T. M. Townes. 1987. Transfer of the metallothionein-human growth hormone fusion gene into channel catfish. Trans. Am. Fish. Soc. 116:87-91.

Ebert, K. M., J. P. Selgrath, P. DiTullio, J. Denman, T. E. Smith, M. A. Memon, J. E. Schindler, G. M. Monastersky, J. A. Viatle, and K. Gordon. 1991. Transgenic production of a variant of human tissue-type plasminogen activator in goat milk. Bio/Technology 9:835-838.

Hammer, R. E., V. G. Pursel, C. E. Rexroad, Jr., R. J. Wall, D. J. Bolt, K. M. Ebert, R. D. Palmiter, and R. L. Brinster. 1985. Production of transgenic rabbits, sheep and pigs by microinjection. Nature 315:680-683.

Ikeda, H., and H. Sugimura. 1980. Fu-4 resistance gene: a truncated endogenous murine leukemia virus with ecotropic interference properties. J. Virol. 63:5405-5412.

Krimpenfort, P., A. Rademakers, W. Eyestone, A. Van der Schans, S. Van den Broek, P. Kooiman, E. Kootwijk, G. Platenburg, F. Pieper, R. Strijker, and H. de Boer. 1991. Generation of transgenic dairy cattle using "in vitro" embryo production. Bio/Technology 9:844-847.

Lo, D., V. Pursel, P. J. Linton, E. Sandgren, R. Behringer, C. Rexroad, R. D. Palmiter, and R.L. Brinster. 1991. Expression of mouse IgA by transgenic mice, pigs and sheep. Eur. J. Immunol. 21:1001-1006.

Murray, J.D., C.D. Nancarrow, J.T. Marshall, I.G. Hazelton, and K.A. Ward. 1989. The production of transgenic Merino sheep by microinjection of ovine metallothionein-ovine growth hormone fusion genes. Reprod. Fert. Devel. 1:147-155.

Nancarrow, C.D., J.T.A. Marshall, J.L. Clarkson, J.D. Murray, R.M. Millard, C.M. Shanahan, P.C. Wynn, and K.A. Ward. 1991. Expression and physiology of performance regulating genes in transgenic sheep. J. Reprod. Fert. Suppl. 43:277-291.

Palmiter, R.D., R.L. Brinster, R.E. Hammer, M.E. Trumbauer, M.G. Rosenfeld, N.C. Birnberg, and R.M. Evans. 1982. Dramatic growth of mice that develop from eggs microinjected with metallothionein-growth hormone fusion genes. Nature 300:611-615.

Pursel, V.G., C.E. Rexroad, Jr., D.J. Bolt, K.F. Miller, R.J. Wall, R.E. Hammer, C.A. Pinkert, R.D. Palmiter, and R.L. Brinster. 1987. Progress on gene transfer in farm animals. Vet. Immunol. Immunopathol. 17:303-312.

Pursel, V.G., C.A. Pinkert, K.F. Miller, D.J. Bolt, R.G. Campbell, R.D. Palmiter, R.L. Brinster, and R.E. Hammer. 1989. Genetic Engineering of Livestock. Science 244:1281-1288.

Rexroad, C.E. Jr. 1992. Transgenic technology in animal agriculture. Anim. Biotech. 3:1-13.

Rexroad, C.E. Jr., R.E. Hammer, D.J. Bolt, K.E. Mayo, L.A. Frohman, R.D. Palmiter, and R.L. Brinster. 1989. Production of transgenic sheep with growth-regulating genes. Molec. Reprod. Dev. 1:164-169.

Rexroad, C.E. Jr., K. Mayo, D.J. Bolt, T.H. Elsasser, K.F. Miller, R.R. Behringer, R.D. Palmiter, and R.L. Brinster. 1991. Transferrin- and albumin-directed expression of growth-related peptides in transgenic sheep. J. Anim. Sci. 69:2995-3004.

Roschlau, K., P. Rommel, L. Andreewa, M. Zacchel, D. Roschlau, B. Zackel, M. Schwerin, R. Huhn, and K.G. Gazarjan. 1989. Gene transfer experiments in cattle. J. Reprod. Fert. 38 (Suppl 1):153-160.

Salter, D.W., E.J. Smith, S.H. Hughes, S.E. Wright, A.M. Fadly, R.L. Witter, and L.B. Crittenden. 1986. Gene insertion into the chicken germ line by retrovirus. Poultry Sci. 65:1445-1458.

Sims, M.M., and First, N.L. 1993. Production of fetuses from totipotent cultured bovine inner cell mass cells. Theriogenology 39:313. (Abstr.).

Swanson, M.E., M.J. Martin, K. O'Donnell, K. Hoover, W. Lago, V. Huntress, C.T. Parsons, C.A. Pinkert, S. Pilder and J.S. Logan. 1992. Production of a functional human hemoglobin in transgenic swine. Bio/Technology 10:557-559.

Velander, W.H., J.L. Johnson, R.L. Page, L.G. Russell, A. Subramanian, T.D. Wilkins, F.C. Gwazdauskas, C. Pittius, and C.V.N. Drohan. 1992. High level expression in the milk of transgenic swine using the cDNA encoding human protein C. Proc. Natl. Acad. Sci. USA 89:12003-12007.

Wall, R.J., R.A. McKnight, A. Shamay, and L. Hennighausen. 1992. Matrix attachment sequences improve genetic control of a mammary gland transgene in mice. Theriogenology 37:319. (Abstr.).

Weidl, U.H., H. Lenz, and G. Brem. 1991. Genes encoding a mouse monoclonal antibody are expressed in transgenic mice, rabbits and pigs. Gene 98:185-191.

Wieghart, M., J.L. Hoover, M.M. McGrane, R.W. Hanson, F.M. Rottman, S.H. Holtzman, T.E. Wagner, and C.A. Pinkert. 1990. Production of transgenic pigs harbouring a rat phosphoenolpyruvate carboxykinase-bovine growth hormone fusion gene. J. Reprod. Fert. Suppl. 41:89-96.

Wilkie, T.M., R.L. Brinster, and R.D. Palmiter. 1986. Germline and somatic mosaicism in transgenic mice. Dev. Biol. 118:9-18.

Wright, G., A. Carver, D. Cottom, D. Reeves, A. Scott, P. Simons, I. Wilmut, I. Garner, and A. Colman. 1991. High level expression of active human alpha-1-antitrypsin in the milk of transgenic sheep. Bio/Technology 9:830-834.

Issues for Institutional Animal Care and Use Committees (IACUCs)

Oversight of the Use of Agricultural Animals in University Teaching and Research[1]

W. Ray Stricklin and Joy A. Mench

INTRODUCTION

The monitoring of agricultural animal research and teaching activities can present some special opportunities and problems for institutional animal care and use committees (IACUCs) at land-grant universities and colleges of agriculture. Monitoring animal agricultural activities often requires an IACUC to deal not only with the routine politics of animal welfare and the ethical dilemmas associated with the use of animals in research, but also with agricultural traditions and the entangled administrative lines of responsibility found in some colleges and universities.

The moral or ethical basis for concern about the treatment of animals should not differ based on research objectives. However, since current regulations cover biomedical research but not food and fiber research, different housing and care criteria for animals of the same species have arisen solely on the basis of the researcher's goals. The goal of much food and fiber research is oriented toward providing abundant and inexpensive food and fiber for all members of society. This situation dictates that animals must be treated according to production standards in order for the research goals to be achieved.

Some agricultural animal research-related problems that IACUCs may have to deal with are, therefore, fundamentally different from the problems encountered in a traditional biomedical program. This may be due to differences in the goals of agriculture, the administrative structure of agricultural research programs, and disagreements about the degree of regulation that is appropriate for agricultural research. The discussion presented herein will therefore include background information about animal agriculture and the funding, conduct, and administration of agricultural animal research and teaching activities.

HISTORY, TRADITION, AND AGRICULTURAL ANIMAL RESEARCH

Colleges of Agriculture within Land-Grant Universities

The Morrill Act of 1862 provided 17.4 million acres of land and nearly $8 million to individual states to enable them to establish universities. The resultant land-grant university

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[1]Portions of this paper were used in the NIH (1992) publication entitled "Laboratory Animal Care and Use Committee Guidebook." This article is published as Scientific Article No. 8218 of the Maryland Agricultural Experiment Station.

system incorporated a uniquely American philosophy of higher education in that it made a university education accessible to students of all income levels, provided financial support for higher education from the federal government, and established a role for the university in teaching a practical as well as a classical curriculum. Each state was to sell its allotment of federal land and use the money generated for the

> ...endowment, support, and maintenance of at least one college where the **leading object** shall be, without excluding other scientific and classical studies, and including military tactics, to teach such branches of learning as are related to agriculture and the mechanic arts, in such manner as the legislatures of the states may respectively prescribe, in order to promote the **liberal and practical education of the industrial** classes in the several pursuits and professions of life (emphasis ours) (First Morrill Act, 1862).

Each state currently has at least one land-grant university. In addition, passage of the 1890 Morrill Act led to the establishment of 17 so-called historically black land-grant colleges in the southern and border states. Today, these campuses serve students of all races, and enroll roughly one-fourth of all African-American students in higher education in the United States (NASULGC, 1989).

Through the Hatch Act of 1887, the Federal Government established the state agricultural experiment station network to ensure that agricultural research oriented to specific geographic regions would be conducted throughout the United States. This was followed by the Smith-Lever Act of 1914, which mandated the third key function of today's state and land-grant universities: extension or public service.

Impact of Agricultural Research

A major goal of the land-grant universities was to lessen the amount of labor required for food and fiber production. Technologies were developed to replace human labor, thereby greatly improving the efficiency of production and providing the abundant and relatively inexpensive food and fiber supply that we enjoy today.

In addition to the desired primary effects, these technologies had many secondary effects, both positive and negative. The crate housing of veal calves and pregnant sows, the high-density caging of laying hens, and the use of automated feeding and watering systems are animal production technologies that are considerably less labor-intensive than "traditional" agricultural practices. These systems have essentially eliminated the long hours of strenuous physical labor once considered part of the routine daily chores done primarily by wives and children before and after the field work. The technologies implemented to reduce labor in food and fiber production, however, also imposed restrictions on the activity and behavior of animals (Mench, 1992a; Mench and van Tienhoven, 1986). The general topic of scientific assessment of the welfare of agricultural animals has been addressed at recent conferences (Mench, 1992b; Mench and Stricklin, 1993; Thompson et al., 1992). Many of the ethical questions surrounding current agricultural production practices center on the economic, bioethical, and environmental costs and benefits of using technology to manipulate plant and animal life for human purposes (Food Animal Well-Being, 1993; Stricklin, 1989a; Stricklin and Swanson, 1993).

Departments of Food and Fiber Research and Teaching

The majority of university-related food and fiber research and teaching is conducted within animal science, dairy science, poultry science, and veterinary science departments (herein referred to generically as animal sciences departments) at land-grant universities. Colleges of veterinary medicine also conduct research that directly or indirectly affects food and fiber production from animals. Animal sciences departments were originally called animal husbandry departments, and faculty frequently espoused the philosophy that good animal husbandry was both an art and a science and also spoke unabashedly of concern for the well-being of animals. A large bronze plaque hangs in the hallway of the Animal Sciences Laboratory Building at the University of Illinois-Urbana on which is reproduced a poem written in 1917 by H.W. Mumford, then Professor of Animal Husbandry, part of which is presented as follows:

> Behold the Stockman!
> Artist and Artisan...
> Whose devotion to his animals is
> second only to his love of God and family.
> Whose gripping affection is tempered only by his
> inborn sense of the true proportion of things.
> Who cheerfully braves personal discomfort to
> make sure his stock suffer not...
> Who sees something more in cows than the drudgery
> of milking,
> more in swine than the grunt and squeal,
> more in the horse than the patient servant, and
> more in sheep than the golden hoof...
>
> (Mumford, 1917)

Many of the earlier animal science educators recognized the need for a strong foundation in scientific knowledge combined with the intangible human elements of empathy and compassion for animals. Dr. Leo Bustad, Professor and Dean Emeritus of Veterinary Medicine at Washington State University, described this viewpoint when discussing his learning experiences in a post-World War II animal husbandry department:

> Happy, contented, and well-cared-for livestock, I was told, were better producers. During my graduate work in nutritional studies on swine my mentor Tony Cunha, a very kind and gentle person, reinforced this attitude. He and Department Chairperson M.E. Ensminger, one of the most renowned animal scientists in the world, visited me and my pigs at odd hours, such as early Sunday morning to be sure the animals were well-cared-for and to assist me in my stewardship (Bustad, 1987).

In the post-Sputnik era of the 1960s, when science and technology gained prominence in American educational institutions, departments changed their names from Animal Husbandry to Animal Science, and accordingly, may have altered their research and teaching philosophies to some extent.

Faculty members within animal sciences departments have responsibilities and a percentage of appointment time divided among three areas: teaching, extension (which refers to the extending of knowledge to members of the general public), and research. The amount of salary and support funding a faculty member in agriculture receives ranges from zero to 100 percent in any one of these three areas. **Teaching** is funded primarily from the state legislature through the traditional university administrative lines of authority (university chief administrator to college dean to department head to faculty member). **Extension** is funded from state and federal sources through the University Extension Service Director, while **research** is funded from state and federal sources generally through the University Experiment Station Director.

MONITORING AGRICULTURAL ANIMAL CARE AND USE

To properly monitor the use of agricultural animals in research and teaching, IACUCs need to use different criteria than those used for biomedical research both in evaluating the appropriateness of protocols and in establishing standards for agricultural research facilities. Agricultural research often has a different target audience than does biomedical research. To be relevant to commercial agricultural production, some agricultural research must be conducted under conditions that are feasible and appropriate for farmers, and that incorporate economic considerations. There are practices that are common in animal agriculture, which would not be permitted under the regulations governing biomedical experiments. In addition, the housing requirements for agricultural animals used in food and fiber research often differ from those of agricultural and laboratory animals used in biomedical research.

Important opportunities can arise from monitoring agricultural research. In particular, the IACUC can provide a forum for increased communication between biomedical and agricultural researchers. We believe that increased communication can have mutual benefits that are frequently overlooked by both groups. In addition to benefiting animals, a quality animal care program is important to the morale of faculty and staff and for maintaining scientific credibility, which benefits all members of an institution.

Standards for Evaluating Animal Research and Teaching

Food and fiber research and teaching activities involving agricultural animals are not covered by either the Animal Welfare Act or the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* (PHS, 1986). However, a *Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching* (*Ag Guide*) (Consortium for Developing a Guide, 1988), patterned on the *Guide for the Care and Use of Laboratory Animals* (*Guide*) (NRC, 1985) but directed specifically toward agricultural research activities, was compiled for the benefit of those institutions that conduct agricultural animal research. This *Ag Guide* was developed by a consortium of scientific and professional organizations, industrial groups, and governmental agencies. The development and writing of the *Ag Guide* occurred in conjunction with a series of consortium committee and subcommittee meetings held during 1986 and 1987, with successive drafts reviewed for comments by an increasingly larger group of interested individuals (Stricklin, 1989b).

The initial draft of the *Ag Guide* was developed from input by six Guide Development Subcommittees representing the major farm animal species-types, with each of these Subcommittees chaired by an animal scientist who had a background and experience in applied ethology. Also, each of the Subcommittees included a veterinarian, an agricultural engineer, an industry representative, and an animal science researcher or educator. Through the review process, the information compiled by the six species-based Guide Development Subcommittees was condensed into a 74-page document by a seven person writing committee. Current practices and issues in commercial animal agriculture were an important consideration when writing the *Ag Guide*.

The *Ag Guide* specifies that the institutional IACUC should include (1) a scientist from the institution with experience in agricultural research or teaching involving agricultural animals; (2) an animal scientist who has appropriate training and experience in the management of agricultural animals and with recognized high professional credentials as verified by scientific and professional societies in animal science, dairy science, or poultry science; (3) a veterinarian who has appropriate training and experience in agricultural animal medicine and is appropriately licensed or eligible to be licensed to practice veterinary medicine; (4) a non-scientist affiliated with the institution; (5) a person not otherwise affiliated with the institution; and (6) other members as may be required by institutional needs and applicable laws, regulations, and policies. Under the *Ag Guide*, the IACUC is required to meet regularly to ensure that agricultural animal use is humane, appropriate, and in accordance with the *Ag Guide*; to review teaching and research protocols; and to conduct semi-annual facilities inspections and reviews of the overall agricultural animal care and use program.

The adoption of the *Ag Guide* by IACUCs is completely voluntary. However, the Council on Accreditation of the American Association for Accreditation of Laboratory Animal Care (AAALAC) has accepted portions of the *Ag Guide* as the basis for accreditation of institutions using agricultural animals in biomedical research. Prior to U.S. Department of Agriculture (USDA) funding of production animal research, a statement must be submitted that an IACUC has approved the proposed research. USDA does not specify

either the *Ag Guide* or the *Guide* as the basis for the protocol review.

Administration of IACUCs

Clearly defined administrative lines of authority for the animal care program are essential in order for IACUCs to function effectively. Because agricultural colleges sometimes receive funding that is separate from that of other colleges, agricultural programs in some universities function with a degree of autonomy that can result in more than one administrator having some authority over portions of animal research within the institution.

The organization of the administration of agricultural programs varies among the land-grant universities. In some universities, the dean of the college of agriculture is also the director of the experiment station and the extension service. In other university systems, the directors may be equivalent in administrative rank to deans or even, on the larger multi-campus systems, to the chief campus administrator.

Because the responsible university officer for agriculture receives funding for research and extension directly from the state and federal government, he or she may be reluctant to relinquish control over agricultural research programs to an IACUC, which receives its authority through the traditional university lines of administration. Animal housing facilities may create an additional complication. In some situations, the buildings in which agricultural animals are housed belong to the administrator responsible for teaching, but are used for experiment station research. Conversely, facilities can be the property of the experiment station (and possibly located at an appreciable distance from the university), but used for campus-funded undergraduate and graduate teaching.

A number of potential problems can result from this administrative complexity. One lies in determining which administrator or administrators are financially responsible for any facility improvements identified by the IACUC. Often the ownership of the animals is the basis used to determine who has financial responsibility for the facilities. A second potential and related problem is in determining whether the administration of the animal care program is best achieved by establishing more than one IACUC.

Under the *Ag Guide*, the agricultural IACUC can be either a separate committee or the same as the IACUC required by the Animal Welfare Regulations (AWRs), provided that the committee composition outlined in the *Ag Guide* is met. At the University of Maryland College Park Campus, there are essentially three committees. The first is the IACUC that is required by the AWRs, which oversees the use of both laboratory and agricultural animals used in "biomedical" research and teaching, as well as all graduate student theses that involve the use of animals. Secondly, there is a subcommittee that makes recommendations to the IACUC on matters related to the care and use of agricultural animals used in food and fiber research and housed in on-campus facilities, and in particular reviews protocols and conducts the facilities inspections for those animals. Thirdly, the Maryland Agricultural Experiment Station has a separate committee that is responsible for overseeing the care and use of agricultural animals housed at off-campus facilities. Although it occurs only rarely, it is possible for a single research project to fall within the jurisdiction of all three of these committees, for example when a graduate student is conducting research using agricultural animals at both on and off-campus sites. Under such circumstances, excellent lines of communication among the different committees and among the appropriate administrators are essential.

Protocol Review and Facility Inspection

Responsible protocol review is one of the most critical functions of IACUCs. A system of protocol review that is consistent and judicious is essential in order to gain and hold the respect and support of the scientists monitored by the IACUC. Currently, however, maintaining consistency when evaluating protocols involving farm animals can be difficult, as it is sometimes unclear whether the IACUC should follow the *Guide* or the *Ag Guide*. For example, does a research protocol involving an animal health issue, such as parasite control in agricultural research animals, which is not funded by the Public Health Service, fall under the *Ag Guide* or the *Guide*?

Consistency in protocol review also requires that the scope of the IACUC be clearly established. It may be difficult to determine whether the IACUC should be responsible for monitoring certain activities, particularly those involving extension functions. For example, extension specialists are sometimes responsible for youth activities, including 4-H Clubs. Should the specialist be required to submit a protocol for the use of animals at county fairs related to youth education? Extension faculty may have graduate students involved in survey-type research that takes place only on privately-owned farms. Should the IACUC have protocol review responsibility for this research, and if so, how can IACUC standards of animal care be enforced? Some agricultural colleges conduct test stations to assess the growth ability of potential breeding animals under standardized conditions. Researchers often "piggy-back" non-invasive research projects on these privately-owned animals. How much control should an IACUC be expected to have over the treatment of these animals even though they are housed within a university facility? Approval of a protocol involving animals within a test-station but rejection of a protocol for animals in a research building, even though both are kept under the same housing and management conditions, would be a perfectly conceivable (but clearly inconsistent) IACUC policy.

In some colleges of agriculture the funding available to improve animal facilities has not kept pace with other programs. In addition, because food and fiber research results must be meaningful to persons whose livelihood comes from agriculture, the facilities in which these animals are housed differ from the environmentally-controlled, hospital-like facilities in which laboratory animals are typically housed. The

inspection of agricultural animal facilities can thus present considerable problems for the IACUC. We believe that it is important for the IACUC to keep in mind that a good animal care program can be maintained even in modest facilities. At the same time, we believe that agricultural personnel cannot use tradition as a justification for not providing appropriate animal care, including properly constructed and maintained facilities.

There are no easy answers to the questions we have posed about protocol review and facility inspection, or at least none that lead to workable solutions. There are differences between food and fiber research objectives and biomedical research objectives that are essential in order for each of the disciplines to function successfully. After dealing with some of the frustrations of monitoring animal agricultural research, however, it may be tempting at times for the IACUC to adopt a strategy oriented toward eliminating the problem program or facility or both. However, although advising faculty and administrators about the appropriateness of program areas and objectives is an IACUC function, the determination of research and teaching areas and objectives is not, and should not become, a function of the IACUC.

Agricultural Animal Technicians and Standards of Care

Farm labor has traditionally been cheap, with migratory workers or farm family members providing much of the work force. Until relatively recently, farm workers were even excluded from the federally mandated minimum wage laws. As a carryover from these general attitudes toward farm workers, university personnel working as technicians and caretakers for agricultural animals in many cases have less education, less training, and lower wages than their colleagues doing equivalent (or even sometimes less demanding) work in animal research laboratories. Within the same institution, farm animal caretakers may be hired who have only a high school diploma (or less), while laboratory animal caretakers are required to have at least a bachelor's degree. Accordingly, levels of awareness and appreciation for the importance of adherence to animal care guidelines can differ. We believe that, because the responsibilities and duties of these animal care personnel do not differ, standardizing hiring criteria and wages would result in a significant improvement in the standards of care for agricultural animals at many institutions.

Opportunities

Animal scientists are descended academically from a discipline, animal husbandry, that was founded to investigate methods of improving the care and well-being of animals. Animal scientists represent an academic discipline that has researched various aspects of nutrition, physiology, reproduction, genetics, growth, and lactation in animals under many different housing and management conditions. We have argued elsewhere that animal scientists can make major contributions to laboratory animal IACUCs (Mench and Stricklin, 1991). On the other hand, the majority of colleges of agriculture are currently in the process of establishing formal IACUC procedures, and can benefit significantly from the experiences of the general IACUC.

CONCLUSION

The monitoring of agricultural animal research and teaching activities can significantly benefit an institution. Establishing and maintaining an animal care program that is consistent across all animals and disciplines can increase the quality of research, collaboration and even faculty and staff morale. We believe that a local, high-quality institutional animal care program has immediate benefits to the institution, which ultimately supports the credibility of the entire scientific community. Beneficial changes in animal care programs are most likely to be accomplished when all parties, the IACUC, the principal investigators, animal care technicians, and university administrators view the monitoring of agricultural animals as being in everyone's best interest.

A major difference between biomedical research and agricultural research is that agricultural animal research must be conducted under conditions representative of agricultural practices. Because of this fundamental difference, standards for agricultural animal research facilities and the review of protocols that have food or fiber production as an endpoint often at times differ from those for laboratory animals. We do not believe, however, that this means that agricultural animals should be viewed by an IACUC using different ethical standards. The purpose of animal care oversight is to ensure animal well-being, and this should be the goal of the IACUC regardless of the type of animal or the funding source of the research.

REFERENCES

Bustad, L. K. 1987. Investigators' interrelationship with laboratory animals. Pp. 167-170 in Effective Animal Care and Use Committees, F. B. Orlans, R. C. Simmonds, and W. J. Dodds, eds. Bethesda, Maryland: Scientists Center for Animal Welfare.

Consortium for Developing a Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching. 1988. Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching. Champaign, Illinois: Association Headquarters (Available at a cost of $5.00 each from Association Headquarters, 309 West Clark Street, Champaign, IL 61820. Tel: 1-217-356-3182).

First Morrill Act. 1862. An Act Donating Public Lands to the Several States and Territories Which May Provide Colleges for the Benefit of Agriculture and Mechanic Arts. Chapter 130, 12 Stat. 503, 7 USC 301-308, July 2.

Food Animal Well-Being. 1993. Conference Proceedings and Deliberations. USDA and Purdue University Office of Agricultural Research Programs. (Available from: Purdue University Office of Agricultural Animal Research Programs, 1140 Agricultural Administration Building, Purdue University, West Lafayette, IN 47907-1140).

Hatch Act. 1887. An Act to establish agricultural experiment stations in connection with the colleges established in the several States under the provisions of the (First Morrill Act). Chapter 314, 24 Stat. 440, 7 USC 361, March 2.

Mench, J. A. 1992a. The welfare of poultry in modern production systems. Poultry Sci. Rev. 4:107-128.

Mench, J. A. 1992b. Rapporteur's report: Animal well-being. Pp. 99-100 FAIR '95 Proceedings, Kansas City, Missouri.

Mench, J. A., and W. R. Stricklin. 1991. Animal care and use committees: Who should serve? ILAR News 33:31-37.

Mench, J. A., and W. R. Stricklin. 1993. An International Conference on Farm Animal Welfare: Scientific Perspectives. J. Agric. Env. Ethics 6(Spec. Suppl. 2):1-116.

Mench, J. A., and A. van Tienhoven. 1986. Farm Animal Welfare. American Scientist 74:598-603.

Mumford, H. W. 1917. A Tribute to the Stockman. Breeders Gazette, Chicago.

National Association of State Universities and Land-Grant Colleges (NASULGC). 1989. Fact Book 1990. Washington, D.C.

National Institutes of Health (NIH). 1992. Institutional Animal Care and Use Committee Guidebook. Public Health Service, NIH. NIH Pub. No. 92-3415.

National Research Council (NRC). 1985. Guide for the Care and Use of Laboratory Animals. A report of the Institute of Laboratory Animal Resources Committee on Care and Use of Laboratory Animals. Washington, D.C.: U.S. Department of Health and Human Services.

Public Health Service (PHS). 1986. Public Health Service Policy on Humane Care and Use of Laboratory Animals. Washington, D.C.: U.S. Department of Health and Human Services. (Available from: Office for Protection from Research Risks, Building 31, Room 4B09, National Institutes of Health, Bethesda, MD 20892).

Second Morrill Act. 1890. An Act to apply a portion of the proceeds of the public lands to the more complete endowment and support of the colleges for the benefit of agriculture and the mechanic arts. Chapter 841, Stat. 417, 7 USC 322 et seq., August 30.

Smith-Lever Act. 1914. An Act to provide for cooperative agricultural extension work between the agricultural colleges in the several States receiving the benefits of an Act of Congress. Chapter 79. 38 Stat. 372, 7 USC 341-349, May 8.

Stricklin, W. R. 1989a. Benefits and costs of animal agriculture. Pp. 87-92 in Proceedings of the Scientists Center for Animal Welfare Symposium on Science and Animals: Addressing Contemporary Issues. H. N. Guttman, J. A. Mench, and R. C. Simmonds, eds. Bethesda, Maryland: Scientists Center for Animal Welfare.

Stricklin, W. R. 1989b. The development of guidelines for the care and use of agricultural animals in agricultural research and teaching. Pp. 44-51 in Animal Care and Use in Behavioral Research: Regulations, Issues, and Applications, J. W. Driscoll, ed. Beltsville, Maryland: Animal Welfare Information Center, National Agricultural Library.

Stricklin, W. R., and J. C. Swanson. 1993. Technology and Animal Agriculture. In An International Conference on Farm Animal Welfare: Ethical, Technological, and Sociopolitical Perspectives. J. Agric. Env. Ethics 6(Spec. Suppl. 1):67-80.

Thompson, P., W. R. Stricklin, P. Siegel, A. Rowan, and B. Rotlin. 1992. Well-being of production animals: A diversity of viewpoints. Pp. 71-80 in FAIR '95 Proceedings. Kansas City, Mo.

In the News

ILAR to Expand Animal Models and Genetic Stocks Information Program

Some of the information most needed by scientists can be the hardest to obtain, including information that allows a scientist to select the most appropriate research model and, if the model is an animal, to find sources of the model and provide appropriate care. For 40 years, the Institute of Laboratory Animal Resources (ILAR) has conducted the Animal Models and Genetic Stocks Information Program, which offers assistance in selecting appropriate models, locating sources of animals, using standardized nomenclature, and interpreting guidelines for humane care and use of animals. It includes the Animals for Research database (a computerized list of sources of animals in the United States and Canada) and the Registry of Laboratory Codes (a computerized list of symbols used with standardized nomenclature of rodents and rabbits to identify institutions that maintain breeding colonies).

To keep pace with technological advances and to make the information more broadly and effectively available to scientists, ILAR proposes to update the Animals for Research database, expand it to include international sources of animals and descriptions of animal models, and make it and the Registry of Laboratory Codes available on-line in a user-friendly format. Easy access to other animal-related databases, a list of publications on animal care and genetic stocks, and a bulletin board to facilitate communication would also be provided. A summary of information in the Animals for Research database would be published annually for users without Internet capability.

The modernized AMGS Program will allow ILAR to provide information critical to the biomedical research effort more effectively and to more people. For more information contact Dr. Dorothy D. Greenhouse, Sr. Program Officer, Institute of Laboratory Animal Resources, National Research Council, 2101 Constitution Ave., NW, Washington, DC 20418. Tel: 1-202-334-2590; Fax: 1-202-334-1687; Internet: dgreenho@nas.edu.

National Information Infrastructure for Biological Research

The rapid growth of electronic research databases provides a major new resource for life scientists in all disciplines, especially when the data are made available via the developing "information superhighway." These new community resources afford the potential for great advances within such disciplines as genetics, structural biology, and ecology.

They also greatly improve capabilities for integrated research across disciplines.

However, the sheer volume of information and the independent development of these databases raise several questions about management, interaction, and accessibility:

- How can the kinds of information needed best be identified and provided?
- How can databases be accessed by those who need the information?
- How should these resources be integrated for more efficient and effective use within and across disciplines?
- To what extent and how should they be standardized to simplify access, data entry, and data retrieval?
- What are the best approaches for ongoing quality control, maintenance, and support of these databases?

A coherent national strategy is needed to address these issues in a timely fashion so that this major new component of our research infrastructure can develop smoothly and effectively.

The National Research Council is planning to establish a committee of experts to develop such a strategy. The eventual goal is an integrated resource of well-maintained key databases that is easily accessible to the scientific community.

The committee will work with various components of the research community to gather the necessary information. As part of this process, the committee will hold a national workshop to explore key issues. The workshop proceedings will be published quickly and widely disseminated (including by electronic dissemination) to stimulate further discussion in the scientific community and to encourage additional input while the committee is developing its report.

The final committee report will be reviewed by scientists and other appropriate experts in a broad range of disciplines. The report will be published as a book and will also be available electronically.

This project is currently in development. For more information contact Dr. Dorothy D. Greenhouse, Institute of Laboratory Animal Resources, National Research Council, 2101 Constitution Ave., NW, Washington, DC 20418. Tel: 1-202-334-2590; Fax: 1-202-334-2687; Internet: dgreenho @NAS.edu.

Biotechnology Forum to Explore Complex Issues

The development of promising biotechnologies and their products create new jobs; promote economic growth; and address global agricultural, environmental, and health concerns. Aquaculture, bioengineering, bioremediation, and renewable resource technologies are emerging throughout the world. Although the opportunities for biotechnology are impressive, unresolved scientific and societal issues confront basic and applied research, technology development, and commercialization of products.

The Board on Biology of the National Research Council is planning to establish a Forum on Biotechnology to bring together leading scientists, administrators, policy-makers, and executives engaged in biotechnology research, development, and commercialization. This collaboration of government, industry, and academia is intended to promote open communication on such issues as regulation and oversight, market development, public perception, environmental effects, research and development, education and training, and coordination of activities. The forum will offer its members a neutral and nonadversarial setting to discuss important biotechnology issues, promote mutual understanding, and develop imaginative approaches to problem-solving.

The Board on Biology is currently seeking funding for this forum. For more information contact Dr. Eric Fischer, Director, Board on Biology and Institute of Laboratory Animal Resources, National Research Council, 2101 Constitution Avenue, NW, Washington, DC Tel: 1-202-334-2215; Fax: 1-202-334-1687; Internet: efischer@nas.edu.

AAALAC Appoints Associate Directors in Response to Expanded Activities

The American Association for Accreditation of Laboratory Animal Care (AAALAC) has appointed associate directors for administration and accreditation in order to continue to expand its activities to meet the needs of the life sciences community and the general public. Dr. Kathryn A. L. Bayne was named Associate Director for Accreditation and Dr. Gerald P. Jaax Associate Director for Administration. As Diplomates of the American College of Laboratory Animal Medicine, both appointees bring broad and varied expertise to AAALAC.

Dr. Bayne will focus on coordinating accreditation activities. She joins AAALAC from her former position as Chief of the Behavior and Nutrition Unit, National Center for Research Resources, Veterinary Resources Program, National Institutes of Health. She holds an M.S. in experimental psychology, a Ph.D. in wildlife biology, and a D.V.M. from Washington State University. Dr. Bayne's interest has focused extensively on developing programs for behavioral and environmental enrichment for animals. She

Kathryn A.L. Bayne

Gerald P. Jaax

has published numerous papers in this regard and is active in local and national laboratory animal and veterinary organizations. Dr. Bayne is also a member of the Institute of Laboratory Animal Resources (ILAR) committee that is preparing the seventh edition of the *Guide for the Care and Use of Laboratory Animals.*

Dr. Jaax, appointed Associate Director for Administration, will be responsible for facilitating AAALAC's mission and expanding administrative objectives. Dr. Jaax comes to AAALAC with 22 years of administrative and management experience. He received his D.V.M. from Kansas State University and currently serves in the U.S. Army Veterinary Corps as the senior laboratory animal veterinarian. In this capacity, he is the Consultant to the Army Surgeon General for Laboratory Animal Medicine. He has directed several animal care programs and is responsible for the Army postgraduate training program in laboratory animal medicine.

Electronic Information Available from AWIC

The Animal Welfare Information Center (AWIC) is compiling an electronic library with full-text animal welfare information that will be updated periodically. It has compiled a collection of documents in WordPerfect 5.1 and ASCII (formatted for DOS systems). As other laws or policies become available and processed electronically, they will be added to the collection. Any suggestions or contributions are welcome, particularly documents already in WordPerfect or ASCII formats.

To receive electronic material, provide one formatted 3½" **high-density** floppy disk for each volume and specify the preferred format. For more information about this program contact AWIC, Fifth Floor, National Agricultural Library, 10301 Baltimore Blvd., Beltsville, MD 20705. Tel: 1-301-504-6212; Fax: 1-301-504-6409; Internet: awic @nalusda.gov.

Coming Meetings

July 1994

12 Wildlife Mammals as Research Models: In the Laboratory Animal Field, San Francisco, California. The Scientists Center for Animal Welfare (SCAW) will sponsor this half-day seminar at the 1994 American Veterinary Medicine Association (AVMA) conference. Topics to be covered include wildlife management in the laboratory, contraceptive research and non-capture methods for studying reproduction in wildlife, marking and tracking, aquatic research, and positive reinforcement training. Veterinarians, researchers, regulatory personnel, members of institutional animal care and use committees, administrators, and others interested in these issues are encouraged to attend. For more information contact SCAW, Golden Triangle Building One, 7833 Walker Drive, Suite 340, Greenbelt, MD 20770. Tel: 1-301-345-3500; Fax: 1-301-345-3503.

27–31 Animal Behavior Society Meeting, Seattle, Washington. The goal of the Animal Behavior Society is "to promote and encourage the biological study of animal behavior in the broadest sense, including studies at all levels of organization using both descriptive and experimental methods under natural and controlled conditions." Presentations at the meeting will be multidisciplinary, ranging across zoology, psychology, and anthropology. Special sessions on applied animal behavior and psychoneuroimmunology will be scheduled. There will be a joint session with the American Society of Primatologists on Thursday, July 28, with an emphasis on the behavior of primates. For more information contact James C. Ha or Carolyn Crockett, Primate Center SJ-50, University of Washington, Seattle, WA 98195. Tel: 1-206-543-1440; Internet: jcha@u.washington.edu or crockett@u.washington.edu.

31 July–4 August International Congress of Vertebrate Morphology, Chicago, Illinois. This will be the first International Congress of Vertebrate Morphology held in North America. It will include contributed papers, plenary speakers, workshops, and symposia on such topics as the functional design of musculoskeletal systems, segmentation in vertebrates, genetics and morphology, adaptations of marine amniotes, and amphibian-amniote transition. For more information contact Sue Herring, Chair, ICVM Organizing Committee, Department of Orthodontics, SM-46, University of Washington, Seattle, WA 98195. Tel: 1-206-543-3203; Fax: 1-206-685-8163; Internet: herring@u.washington.edu.

August 1994

4–5 Sharing Animal Welfare Responsibilities Between Affiliated Institutions, Portland, Oregon. This workshop, sponsored by the National Institutes of Health, Office for Protection from Research Risks and by the Department of Veterans Affairs in Portland, Oregon will explore the relationships among academia, government, and industry as they pertain to the care and use of laboratory animals and animal research facilities and programs. The focus of the workshop will address such issues as (1) sorting out collaborations and assuming responsibility, (2) the Veterans Administration vs. academia, (3) costs and benefits of industrial contracts and

agreements, (4) building a shared institutional animal care and use committee (IACUC), and (5) the regulatory agencies' perspective and oversight. This workshop is open to institutional administrators, members of IACUCs, laboratory animal veterinarians, investigators, technicians, and anyone sharing responsibility for management of a sound institutional animal care and use program. For more information contact Ms. Margaret Doherty, Veterans Affairs Medical Center, P.O. Box 1034, Portland, OR 92707-1034. Tel: 1-503-220-8262 ex. 7610; Fax: 1-503-273-5351.

8–12 Pathology of Laboratory Animals, Bethesda, Maryland. This 5-day course, offered at the Uniformed Services University of the Health Sciences, will provide a comprehensive overview of the gross and histopathological manifestations of disease in laboratory species, including rodents, rabbits, nonhuman primates, aquatic animals, and birds. Selected topics in clinical and ultrastructural pathology are also included, and an emphasis is placed on the recognition and interpretation of spontaneous lesions in laboratory animals. This course is designed for veterinarians who are either training or certified in veterinary pathology and laboratory animal medicine. For more information contact Uniformed Services University of the Health Sciences, 14th and Alaska Avenues, N.W., Washington, DC 20306-6000. Tel: 1-301-427-5231; Fax: 1-301-427-5001.

September 1994

29–30 Use of Animals in Research and Alternatives, New Orleans, Louisiana. This workshop is cosponsored by the National Institutes of Health, Office for Protection from Research Risks; the Louisiana State University Medical School; and Xavier University of Louisiana. It will address various aspects of the use of animals in research and education, including the adequacy of computer searches; National Institutes of Health, U.S. Department of Agriculture, and Food and Drug Administration initiatives in alternatives; occupational health; and the role of animals and alternatives in education. For more information contact Ms. Lois Herbez, Administrative Secretary, Louisiana State University Medical Center, 1542 Tulane Avenue, New Orleans, LA 70112. Tel: 1-504-568-4198; Fax: 1-504-568-4843.

October 1994

20 The Husbandry and Care of Birds in the Laboratory, Pittsburgh, Pennsylvania. The Scientists Center for Animal Welfare (SCAW) will sponsor this seminar at the American Association for Laboratory Animal Science's (AALAS's) Forty-fifth Annual Meeting. The seminar will address issues concerning the well-being of many bird species used in laboratory and in field research. Current regulations and guidelines do not always provide enough guidance to investigators, animal care givers, and animal care and use committees. Raptors, passerines, poultry, psittacines, pigeons, and quail will be among the species covered. Researchers, regulatory personnel, members of animal care and use committees, administrators, and others interested in these issues are encouraged to attend. For more information contact SCAW, Golden Triangle Building One, 7833 Walker Drive, Suite 340, Greenbelt, MD 20770. Tel: 1-301-345-3500; Fax: 1-301-345-3503.

November 1994

2–4 Lessons from Animal Diabetes: International Workshop IV, Omiya, Saitama, Japan. This workshop will be a satellite symposium of the Fifteenth International Diabetes Federation Congress. The program will include plenary lectures and poster sessions on topics relating to insulin-dependent diabetes mellitus, non-insulin-dependent diabetes mellitus, transgenic animals, complications, therapeutic interventions, and other topics. For more information contact Symposium Secretariat, Lessons from Animal Diabetes Workshop (LAD IV) c/o Access Brain Inc., Hongo-sky Bldg. #503, Hongo 3-38-11, Bunkyo-ku, Tokyo, Japan 113. Tel: 81-3-3818-7799; Fax: 81-3-3818-4433.

7–9 Fifth Workshop on Mouse Liver Tumors, Arlington, Virginia. This is the latest in a series of workshops by the International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute (HESI). Scientists from academic, government, and industry laboratories will describe emerging research findings on mouse liver carcinogenesis, propose research directions and topics, and suggest approaches for integrating current information into the risk assessment framework. This workshop is likely to be of special interest to the regulatory community. For more information contact Ms. Gretchen Bretsch, HESI, 1126 Sixteenth Street, NW, Washington, DC 20036. Tel: 1-202-659-0074; Fax: 1-202-659-3859.

December 1994

1–2 New Frontiers in Surgery, Charleston, South Carolina. This workshop is cosponsored by the National Institutes of Health, Office for Protection from Research Risks (OPRR) and the Medical University of South Carolina. It will address ethics, protocol review, and technical and training aspects related to new surgical and interventional technologies. Topics to be discussed in the program include xenographic procedures, fetal intervention, transgenic technologies, and the use of biomaterials in orthopedic surgery. As part of a series of workshops sponsored by OPRR on implementing the *Public Health Service Policy on Humane Care and Use of Laboratory Animals*, this workshop is open to institutional administrators, members of institutional animal care and use committees, investigators, and other institutional staff who have responsibility for high-quality management of sound institutional animal care and use programs. For more information contact M. Michael Swindle, D.V.M., MUSC/Comparative Medicine, 171

Ashley Avenue, Charleston, SC 29425-2211. Tel: 1-803-792-3625; Fax: 1-803-792-9067.

8–9 Current Issues and New Frontiers in Animal Research, San Antonio, Texas. The Scientists Center for Animal Welfare (SCAW) and the University of Texas Health Science Center at San Antonio will cosponsor this 2-day conference. The first session will address issues pertaining to institutional animal care and use committees (IACUCs), including a U.S. Department of Agriculture update on regulations and litigation; protocol review issues; how and why IACUCs should develop a code of ethics; confidentiality and the IACUC; and biotechnology's effect on IACUCs. The second session will address biocontainment, biosafety, and biohazards and will include discussions on enrichment and biocontainment issues, biocontainment research, biosafety issues, and methods of biocontainment. The final session, New Frontiers, will include discussions of zoonoses, lab animal behavior, opportunities for alternatives, and xenotransplantion. Researchers, regulatory personnel, veterinarians, members of animal care and use committees, administrators, and others interested in these issues are encouraged to attend. For more information contact SCAW, Golden Triangle Building One, 7833 Walker Drive, Suite 340, Greenbelt, MD 20770. Tel: 1-301-345-3500; Fax: 1-301-345-3503.

June 1996

19–26 Sixth FELASA Symposium on International Harmonization of Laboratory Animal Husbandry Requirements, Basel, Switzerland. The aim of this symposium is to exchange useful information among scientists and regulatory agencies in order to increase our knowledge and harmonize the requirements of laboratory animal husbandry. For more information, contact Sixth FELASA Symposium, Kongresszentrum Messe Basel, Messeplatz 21, CH-4021 Basel, Switzerland. Tel: 61-686-2828; Fax: 61-686-2185.

November 1996

3–7 Second World Congress on Alternatives and Animal Use in the Life Sciences, Utrecht, The Netherlands. The aim of this congress is to exchange information on recent developments in the field of alternatives (replacement, reduction, refinement) within the various areas of animal use, such as toxicology, pharmacology, pharmacy, cancer research, bioassays, and safety testing. Alternatives in education and training, ethical aspects of animal use, and developments aiming at the improvement of animal welfare will be covered. For more information contact World Congress Alternatives 1996, FBU Congress Agency, P.O. Box 80.125, 3508 TC Utrecht, The Netherlands. Tel: 31-30535044; Fax: 31-30533667.

New Books

Clinical Veterinary Microbiology, P. J. Quinn, M. E. Carter, B. Markey, and G. R. Carter. This color-illustrated reference provides readers with concise information on the materials and methods used in bacteriology, mycology, and virology. Practical guidance is given on the collection of diagnostic specimens and isolation and culture of pathogenic micro-organisms, with notes on biochemical and serological tests used to identify microbial pathogens. Detailed descriptions of the aetiology and presenting signs of diseases affecting all of the domesticated species are included. Wolfe Publishing, 1994, 648 pp., hardcover, ISBN 0-7234-1711-3.

A Colour Atlas of Anatomy of Small Laboratory Animals, Peter Popesko, Viera Rajtová, Jindrich Horák. This useful reference discusses the five principal species of mammals used in biomedical research. The two-volume set covers the rabbit, guinea pig, mouse, rat, and hamster. It permits comparisons between closely related species and highlights morphological differences of clinical significance. Detailed contents and illustrations grouped by body regions enable scientists to locate material rapidly. CRC Press, Inc., 1992, 255 pp. (Volume I), 251 pp. (Volume II), hardcover, $180.00 (each), ISBN 0-7234-1822-5 and ISBN 0-7234-1823-3.

Food Animal Well-being 1993: Conference Proceedings and Deliberations, U.S. Department of Agriculture and Purdue University Office of Agricultural Research Programs. This book contains presented papers and summaries of workshop deliberations from the Food Animal Well-Being Conference and Workshop held at Purdue University in West Lafayette, Indiana in 1993. The conference focused on topics that might aid in assuring an appropriate climate for food animal agriculture to prosper, retaining economic viability without sacrificing social acceptability. Presented papers include Animal Production and the New Social Ethic for Animals; Assessing Animal Well-Being: Common Sense, Uncommon Science; Animal Welfare—Politics or Facts?; and Future Impact of New Science and Emerging Technologies on Animal Well-Being. 1993. 139 pp., paperback, $6.00, ISBN 0-931682-36-3. (Available from: Purdue University Office of Agricultural Research Programs, 1140 Agricultural Administration Building, Purdue University, West Lafayette, IN 47907-1140.)

In the Name of Science: Issues in Responsible Animal Medicine, F. Barbara Orlans. This book analyzes the social, political, and ethical conflicts surrounding the use of ani-

mals in scientific experiments. The author examines the history of institutionalized experimentation, current attitudes and ethical arguments on both sides of the issue, different mechanisms for oversight of animal experiments, alternatives to the use of whole animals, animal review committees, animal testing, and the use of animals in education. It concludes with the author's recommendations for future progress. Oxford University Press, 1993, 304 pp., hardcover, $39.95, ISBN 0-19-507043-7.

Lessons from Animal Diabetes IV, Eleazar Shafrir. This is the fourth volume in the *Lessons from Animal Diabetes* series. In contrast to previous volumes, which included the lectures and discussions of international workshops, Volume IV comprises invited reviews on subjects of contemporary interest in experimental diabetes. It will continue the merited reputation of the series for well-edited up-to-date information, much of it original. The 'lessons' concept is a forward-looking approach to diabetes research challenging the diabetologist to integrate current advances in life sciences experimental research using animal models and spontaneous animal diabetes—including the breakthrough areas of immunogenetics and molecular biology—to the practice of therapy and preventive medicine. Smith-Gordon, 1993, 251 pp., hardcover, ISBN 1-85463-077-6.

Publications Available

Single copies of the following publications are available without charge from the institute of Laboratory Animal Resources (ILAR), National Research Council, 2101 Constitution Avenue, NW, Washington, DC 20418. Tel: 1-202-334-2590; Fax: 1-202-334-1687.

Annotated Bibliography on Uncommonly Used Laboratory Animals: Mammals. 1986

Control of Diets in Laboratory Animal Experimentation. 1978

*__Definition, Nomenclature and Conservation of Rat Strains.__ 1993

Guide to Infectious Diseases of Guinea Pigs, Gerbils, Hamsters, and Rabbits. 1974

Important Laboratory Animal Resources: Selection Criteria and Funding Mechanisms for their Preservation. 1990

Laboratory Animal Management: Cats. 1978

Laboratory Animal Management: Genetics. 1979

Laboratory Animal Management: Nonhuman Primates. 1980

Laboratory Animal Medicine: Guidelines for Education and Training. 1979

Long-Term Holding of Laboratory Rodents. 1976

Principles and Guidelines for the Use of Animals in Precollege Education. 1989

Recommendations for the Care of Amphibians and Reptiles in Academic Institutions. 1991.

*__Standardized Nomenclature for Transgenic Animals.__ 1993

Third International Registry of Animal Models of Thrombosis and Hemorrhagic Diseases. 1988

Your Career in Veterinary Technology. AVMA Brochure. Updated Dec. 1989

The following ILAR and Board on Agriculture publications, for which there is a charge, can be ordered from the **National Academy Press, P.O. Box 285, Washington, DC 20055. Tel: 1-202-334-3313 or 1-800-624-6242; Fax: 1-202-334-2451.** All orders must be prepaid by check, money order, or credit card unless accompanied by a bona fide purchase order. Please add $3.50 per item for shipping and handling. Quantity discounts are as follows: 5-24 copies of one title—15%; 25-499 copies of one title—25%. To be eligible for a discount, all copies must be shipped and billed to one address. Please note that the following prices are those for the United States, Canada, Puerto Rico, and Mexico and are subject to change without notice. Ordering information outside these areas can be obtained from the National Academy Press at the address above, or at any of the following locations:

United Kingdom and Western Europe: Plymbridge Distributors Limited, Estover, Plymouth PL6 7PZ, United Kingdom. Tel: 44(0752) 695745; Fax: 44(0752) 695699

Japan: Maruzen Co., Ltd., P.O. Box 5050, Tokyo International 100-31, Japan (accept letters only)

Brunei, People's Republic of China, Hong Kong, India, Indonesia, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand: World Scientific Publishing Co. Pte. Ltd., Farrer Road, P.O. Box 128, Singapore 9128. Tel: 65-3825663; Fax: 65-3825919.

To obtain single copies of the *Guide for the Care and Use of Laboratory Animals* (1985) write **Office for Protection from Research Risks, Division of Animal Welfare, National Institutes of Health, Building 31, Room 5B59, 9000 Rockville Pike, Bethesda, MD 20892.**

* New Publications

Dogs. Laboratory Animal Management Series. 1994.

Rodents. Laboratory Animal Management Series. In press.

Recognition and Alleviation of Pain and Distress in Laboratory Animals. 1992. $29.95. ISBN 0-309-04275-5

Education and Training in the Care and Use of Laboratory Animals: A Guide for Developing Institutional Programs. 1991. $11.95 each; $10.50 if purchasing 2-9 copies; $9.95 if purchasing ten or more copies. ISBN 0-309-04382-4

Infectious Diseases of Mice and Rats. 1991. $60.00. ISBN 0-309-03794-8

Companion Guide to Infectious Diseases of Mice and Rats. 1991. $12.00 each (free with purchase of Infectious Diseases of Mice and Rats). ISBN 0-309-04487-1

Immunodeficient Rodents: A Guide to Their Immunobiology, Husbandry, and Use. 1989. $29.95. ISBN 0-309-03796-4

Use of Laboratory Animals in Biomedical and Behavioral Research. 1988. $14.95. ISBN 0-309-03839-1

Nutrient Requirements of Laboratory Animals. 3d rev. ed. 1978. $12.95. ISBN 0-309-02767-5

Amphibians. Guidelines for the Breeding, Care, and Management of Laboratory Animals. 1974. $29.75. (photocopy of original, bound in paper cover). ISBN 0-309-00151-0

Nutrient Requirements of Domestic Animals: A Series - contact the National Academy Press for information on specific reports and prices.

The following ILAR publications are available from the **National Technical Information Service, 5282 Port Royal Road, Springfield, VA 22161**. Add $3 to the total order for the cost of shipping and handling.

Techniques for the Study of Primate Population Ecology. 1981. Paper cover $31.00. Accession no. PB82 183120

National Survey of Laboratory Animal Facilities and Resources, Fiscal Year 1978. 1980. $17.00 Accession no. PB83 181347

INSTITUTE OF LABORATORY ANIMAL RESOURCES

Volume 36, Number 2 Spring 1994 National Research Council

Farm Animals in Biomedical Research—Part Two

The Goat as a Model for Biomedical Research and Teaching

Issues for Institutional Animal Care and Use Committees (IACUCs)

Integrating Agricultural and Biomedical Research Policies: Conflicts and Opportunities

Commentary: Farm Animal Use in Biomedical Science—Melding the Guidelines

A quarterly publication for biomedical investigators, laboratory animal scientists, institutional officials for research, and members of animal care and use committees.

The Institute of Laboratory Animal Resources (ILAR) was founded in 1952 under the auspices of the National Research Council, National Academy of Sciences, which serves as an independent adviser to the federal government on scientific and technical questions of national importance. Jointly administered by the National Academy of Sciences and the National Academy of Engineering, the National Research Council brings the resources of the entire scientific and technical community to bear on national problems through its volunteer advisory committees.

ILAR is a component of the Commission on Life Sciences. Among its goals are to develop and make available scientific and technical information on laboratory animals and other biologic research resources to the federal government, the laboratory animal science and biomedical research communities, and the public. Guidelines developed by ILAR form a foundation for institutional and governmental policies on animal care and use.

ILAR News is published quarterly by the Institute of Laboratory Animal Resources, National Research Council, 2101 Constitution Avenue, NW, Washington, DC 20418. It is circulated by request to investigators in the field of biomedical and related research.

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All articles in *ILAR News* are peer-reviewed and approved by the Editorial Panel prior to publication. Opinions expressed in this journal are not necessarily those of the Institute of Laboratory Animal Resources, National Research Council/ National Academy of Sciences.

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ILAR NEWS

INSTITUTE OF LABORATORY ANIMAL RESOURCES

VOLUME 36, NUMBER 2 SPRING 1994

CONTENTS

The Goat as a Model for Biomedical Research and Teaching

Linda K. Fulton, Melody S. Clarke, and Harold E. Farris, Jr.

INTRODUCTION

Goats are gaining acceptance as an established model for biomedical research and for surgical training and teaching. They are used in medical, orthopedic, psychological, chemotherapeutic, and physiologic research (Lincicome and Hall, 1984). Goats can be gentle, easy to handle and transport, intelligent, affectionate, friendly, and clean, and they appear to be hardier than other members of the ruminant family. Goats range in average adult size from the small Pygmy goat (40 lbs) to the larger Nubian (170 lbs) or Saanen (200 lbs) (Bliss et al., 1984; Sinn, 1992). Compared with cattle, their small size permits goats to be maintained in a relatively small area. Of the more than 60 breeds of goats in the world, the most popular dairy breeds in the United States are Alpine, La Mancha, Nubian, Oberhauslie, Saanen, and Toggenberg. Goats bred primarily for meat production include the Boer and Spanish (or brush) goat. The African Pygmy and the Nigerian Dwarf goats are generally used as companion animals (Sponenberg, 1993). The smaller size of the Dwarf and Pygmy goats may allow these breeds to be housed more easily than some of the larger breeds.

Several naturally occurring diseases in goats make them suitable animal models for the study of some human diseases. Goats infected with the caprine arthritis encephalitis virus (CAEV) are used as a natural disease model for chronic rheumatoid arthritis of humans (Tenorio et al., 1992). CAEV is a retrovirus related to the HIV retrovirus (Phelps and Smith, 1993). Myotonia congenita occurs in different breeds of goats, which are used as experimental models for studies on human myotonia (Basnur and Yadav, 1990). Pygmy goats are considered to be good antibody producers in immunological research (Lincicome and Hall, 1984).

Due to public sentiment and increasing costs associated with using dogs, some veterinary schools and physician training programs have replaced the dog with the goat in surgical training labs. The goat has been used extensively as an animal model for biomaterials research, teaching, and testing at this institution. Recent literature has described the importance of the development of transgenic farm animals. Preliminary research has focused on altering phenotype to increase the animal's growth rate and carcass composition. New technology is being pursued with the goal of creating a transgenic small ruminant capable of producing large quantities of human pharmaceuticals through synthesis of recombinant proteins excreted though the milk. (Ebert, 1993; Rexroad,1994).

These Nubian goats are intelligent, friendly, and affectionate animals that actively seek human attention. Frequent interactions between animal care personnel and goats increase the general well-being of these animals.

Linda K. Fulton, M.S., D.V.M., Melody S. Clarke, B.S., LATg, and Harold E. Farris, D.V.M., M.S. are with the Department of Research Services, Clemson University, Clemson, South Carolina.

SOURCE OF GOATS FOR BIOMEDICAL RESEARCH

If a commercial source of specific-pathogen-free goats is not available, good quality disease-free goats can most easily be obtained by establishing a working relationship with conscientious local dairy goat producers, who are often interested in expanding their markets beyond the traditional dairy and meat market. Few goat farmers operating a solely commercial dairy enterprise are capable of generating enough income to be self-sustaining (Guss and Ace, 1984). Nevertheless, the popularity of goats as dairy animals is constantly increasing. In 1989, nearly 5,000 bucks (intact males) and 30,000 does (usually breeding females) were registered by the American Dairy Goat Association (Donoghue and Kronfeld, 1990). These figures do not take into account the numbers of castrated male goats (wethers). Dairy goat kids are normally raised by hand and bottle-fed, thereby producing a very docile animal accustomed to frequent human handling. Dehorning or disbudding is a routine management practice in dairy herds for easy handling and housing. Disbudding is usually done between 3 and 7 days of age. Castration and descenting when only a few days old eliminates the unpleasant odor associated with intact male goats (Williams, 1990).

A simple health certificate does not guarantee healthy, disease-free goats. In establishing a source herd, primary consideration should be given to locating closed herds. Goat herds that are accredited and certified free of tuberculosis and brucellosis have been regularly tested negative for these diseases. Many quality dairies are also establishing herds of animals that have been regularly tested negative for caprine arthritis encephalitis virus (CAEV). With the consent of the owner, the herd veterinarian may be consulted for morbidity and mortality data and results of screening tests on the herd. These data will provide valuable information concerning the health status of the herd. Periodically visiting the source herd can also help ascertain herd management practices and the health status of potential research animals.

Once a suitable herd is identified, the vendor should assure that prior to procurement, animals are castrated, dehorned, and identified by ear tattoos at an early age using proper techniques (Williams, 1990). These animals should also be vaccinated against *Clostridium perfringens*, Types C and D; tetanus (Smith and Sherman, 1994, p. 568); and rabies in areas where rabies is endemic (Freeman, 1992).

QUARANTINE, STABILIZATION, AND DISEASE CONTROL

Once the animals arrive at the research facility, they should be quarantined for at least 2 to 3 weeks to allow for stabilization and monitoring of health status (Robinson,1983; Smith, 1990). On arrival, animals should be given a routine physical examination (Smith and Sherman, 1994, pp. 8–13), which should include

- digital palpation of external lymph nodes to be sure there are no abscesses;
- examination of the oral cavity and mouth to be sure they are free of ulcers and sores;
- examination of the eyes for evidence of conjunctivitis;
- examination of the nares (a bilateral, serous nasal discharge may be normal, but a mucopurulent discharge is likely to be a sign of upper or lower respiratory disease);
- examination of the perineal region for evidence of diarrhea;
- inspection of the feet and joints for evidence of enlarged joints and overgrown hooves;
- inspection of skin for ringworm and external parasites (lice are very common).

In addition, stool samples should be analyzed and blood drawn to determine packed-cell volume and total protein. At this institution after the completed examination, a collar with an identification number matching the tatoo is placed on the goat.

Any changes in diet should be made gradually. If dietary changes are necessary, all newly acquired animals should be closely monitored for development of conditions such as clostridial enterotoxemia (Consortium for Developing a Guide, 1988). During the quarantine period, all animals should be monitored and treated as necessary for internal and external parasites. It has been recommended that newly acquired animals be routinely dewormed before allowing them access to common pastures or lots where other goats are maintained (Smith, 1990). Alternatively, fecal flotations using concentrated sugar solutions should be routinely performed and anthelmintics administered based on specific parasites present, fecal egg counts, and numbers of coccidia oocysts (Blackwell, 1983; Freeman, 1992; Smith, 1984). Any animal over one month of age not previously vaccinated should be vaccinated with tetanus toxoid and *Clostridium perfringens*, Types C and D on arrival and again 3 to 4 weeks later (Ayers,1984; Hall, 1976; Williams,1984). Vaccination against rabies should also be considered (Freeman, 1992).

DISEASES OF GOATS

Goats are susceptible to a variety of bacterial, viral, parasitic, and metabolic diseases. Those of major importance are briefly discussed below. Most pharmaceuticals available for treatment of these problems are not labeled for use in goats. All treatments should be initiated only after consultation with the attending veterinarian and as allowable in view of the specific goals of the protocol. Special mention of zoonotic concerns will be made where appropriate.

Respiratory diseases are not uncommon ailments for goats (Robinson, 1983; Smith and Sherman, 1994, Pp. 247-273). Most respiratory problems are associated with the bacteria *Pasteurella* and a variety of *Mycoplasma* species, as well as with viral agents. Poor ventilation, crowding, and

stress related to transportation may contribute to the development of respiratory diseases. Pasteurella infections are mainly caused by *Pasteurella hemolytica*, a gram-negative coccobacilli. Mycoplasmal infections in goats are caused by members of the *Mycoplasma mycoides* group, which include *Mycoplasma mycoides ssp. capri*, *Mycoplasma mycoides ssp. mycoides* (large colony type), and the most virulent F38-like strains (Simecka et al., 1992). Antibiotics should be given based on the results of culture and sensitivity testing. Otherwise, the newer third generation cephalosporins (Naxcel®, Upjohn) can be administered for suspected *Pasteurella*. Tetracyclines or tylosin could be administered if *Mycoplasma* is suspected (Robinson, 1983).

Enteritis caused by *Clostridium perfringens*, type D may be seen primarily in young, rapidly growing animals and is associated with overeating. While sudden death may occur, affected animals may exhibit diarrhea or central nervous system disorders. Treatment consists of administration of clostridium type D antitoxin and supportive fluid therapy. Vaccination and control of feed intake will help prevent the occurrence of enteritis (Blackwell, 1983).

Johne's disease is an enteric infection characterized by chronic wasting, caused by *Mycobacterium paratuberculosis*. Clinical signs are evident in animals two years of age and older. While there is no treatment available, agar gel immunodiffusion tests are available to screen animals for the infection (Freeman, 1992; Sherman, 1989; Smith, 1990; Smith and Sherman, 1994, p.310). Whenever possible, animals that test positive for Johne's disease should be culled from the herd.

Parasitic infections are the major causes of gastrointestinal problems in goats. Nematode and protozoal parasites are found in goats of all ages and can be most troublesome during stressful periods such as after transportation. Fecal exams should be performed routinely and anthelmintics administered accordingly on a schedule that will vary depending on how the animals are housed. Animals maintained in pastures, for example, might require fecal exams and deworming as often as every 14 to 21 days. A fecal exam should be performed routinely on any goat with signs of diarrhea. Routinely removing feces from animal pens, minimizing stressful and crowded conditions, and housing goats on raised, expanded metal, vinyl coated flooring will minimize animal contact with feces and help control intestinal parasites. At this institution the goats housed indoors on raised flooring average a ten percent value increase in packed-cell volumes. In general fecal flotation tests for nematodes are negative for these goats, compared with pastured goats receiving periodic dewormings based on fecal results.

Goats can be infected with the protozoa cryptosporidia, which can cause diarrheal disease in humans, and this is of special concern for immunocompromised humans. Currently there are no specific antiprotozoal agents effective against cryptosporidia. Goats can also be infected with toxoplasma, a protozoa that is best controlled by preventing cats (the definitive host) from entering areas where goats are housed or fed (Foreyt, 1990; Smith, 1990). Cats have also been identified as nonclinical carriers of cryptosporidia (Burrows, 1994).

Q-fever is caused by *Coxiella burnetti*, which causes a subclinical infection in most animals. Q-fever is a serious zoonotic disease. In humans it is characterized by influenza symptoms, fatal hepatitis, or endocarditis. People who work with pregnant animals or conduct necropsies are most at risk of contracting the disease. Animals can be tested on arrival at the research institution and again 2 weeks later to identify infected animals (Smith, 1990; Robinson, 1983). False negative results may be obtained from serology; therefore, all animals should generally be handled as if they are possibly infected with this organism. The use of protective clothing and proper sanitation should be stressed particularly when working with seropositive or peripartuient animals (Singh and Lang, 1985).

Pinkeye is caused by mycoplasmal or chlamydial agents and can result in severe lacrimation, blepharospasm, corneal opacity and ulceration, and temporary or permanent blindness. Although treatment may not eliminate the disease in carrier animals, symptoms will improve with systemic treatment of oxytetracycline and intraocular ophthalmic ointments. An effective program to control flies and dust in the areas where goats are housed as well as treating all incoming animals with systemic and intraocular tetracyclines can help control the spread of pinkeye (Freeman, 1992; Smith, 1990).

Caseous lymphadenitis is a highly contagious infection caused by *Corynebacterium pseudotuberculosis* and is characterized by abscesses in internal and external lymph nodes. Confirmation of infection is based on isolation of the causative agent. An ELISA test is available. All animals entering the research facility should be inspected for evidence of enlarged lymph nodes, abscesses, and scarring from past abscess rupture. Animals exhibiting these signs should not be accepted. If the signs of caseous lymphadenitis appear after arrival and it is inappropriate to cull the affected animal, it should be isolated and the abscess should be drained or removed surgically using proper precautions (Smith and Sherman, 1994, p. 48). Antibiotics are ineffective. There are reports of humans becoming infected with contaminated material; therefore, suitable precautions should be taken when handling suspected cases (Fubini, 1983).

Urolithiasis may be observed in male or female goats (Smith, 1994, pp. 398–404). This condition is a special concern for male goats, as the calculi can block the lower urinary tract and lead to possible bladder rupture. Since the urethral diverticulation in male goats makes catheterization impossible, surgical intervention is needed. The condition of struvite uroliths may be prevented by assuring that the ratio of calcium to phosphorus in the diet is approximately 2:1–2.5:1 (Smith, 1994, p. 402). Adequate roughage should also be available (Nelson, 1984), and good quality grass hay such as fescue or coastal bermuda should be offered ad libitum. If alfalfa or other legume hay is fed to adult goats, special attention should be directed to the effect on the total dietary protein and the calcium-phosphorous ratio. Clean fresh wa-

ter should be available at all times. Adding salt to the ration will increase water consumption and diuresis. Uroliths of varying compositions are possible, and all stones should be analyzed and adjustments in dietary and management procedures should be made accordingly.

Polioencephalomalacia is a disease caused by an imbalance of the production or destruction of thiamine. Affected animals may exhibit neurologic signs including "stargazing", blindness, teeth grinding, ataxia, and opisthotonos. The disease can be treated by administering thiamine. Amprolium, which is often given to control infection by coccidia, should not be used for prolonged periods as it has thiaminase properties (Freeman, 1992).

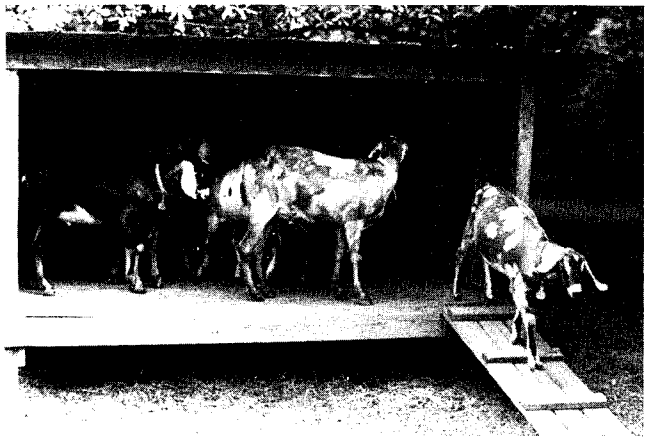
Contagious ecthyma, commonly called orf, is a viral infection that is characterized by epidermal lesions primarily on the face and lips of infected animals. Vaccination is available and recommended annually for infected herds. People who handle infected animals are at risk of acquiring the infection, and precautions should be taken whenever goats exhibit clinical signs of contagious ecthyma (Crandell, 1986).

Caprine arthritis encephalitis virus (CAEV) is a retrovirus of major concern, characterized by chronic nonresponsive arthritis and mastitis in adult goats and encephalitis in young goats. Interstitial pneumonia has been associated with CAEV. Seroprevalence of CAEV in the United States has been reported to be as high as 80 percent. Voluntary elimination has been undertaken in some herds, and animals should be acquired from herds with a record of multiple negative tests. Agar gel immunodiffusion (AGID) and enzyme-linked immunosorbent assay (ELISA) tests are available, of which the ELISA test is considered more sensitive (Bulgin, 1990; Smith, 1990; Smith and Sherman, 1994, p. 78).

HUSBANDRY, ENVIRONMENTAL, AND SOCIAL CONSIDERATIONS

A sound physical examination should be performed 2 weeks after goats begin the quarantine period. Hooves should be inspected and trimmed monthly (Smith, 1983; Smith, 1990). Deworming should be based on routine fecal examinations and packed cell and total protein determinations scheduled at least every 2 months. Vaccination boosters should be repeated annually and goats should be tested at least yearly for tuberculosis, brucellosis, and CAEV (Bliss,1984).

Guidelines for housing goats have been published in the *Guide for the Care and Use of Laboratory Animals* (*Guide*) (NRC, 1985) and in the *Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching* (*Ag Guide*) (Consortium for Developing an Guide, 1988). Goats used in biomedical research and teaching are covered under the provisions of the federal Animal Welfare Act (9 CFR 1–3) and are regulated by the U.S. Department of Agriculture. Such research and teaching activities are subject to prior review and approval by the institutional animal care and use committee. Traditional facilities used for agricultural research and teaching may not be appropriate for goats used in biomedical research and teaching. Specific regulations covering goats and other farm animals under the Animal Welfare Act are pending. It is recommended that evaluation of facilities and programs for goats used in biomedical research should be based on the more stringent guidelines in the *Guide*.



Hutches with three sides and a roof provide adequate shelter from wind and rain. Hutches can be placed directly on the ground, but goats seem to prefer a floor raised above the ground.

Because goats are very social animals and have a strong social hierarchy, they should be housed in groups whenever possible. The addition of several goats to an established herd is less stressful than the addition of single animals. If it is necessary to pen goats individually, a companion goat should be penned nearby so that visual contact and preferably nose-to-nose contact is possible. Pens manufactured of chain link or vertical slots or bars are often used (Consortium for Developing a Guide, 1988; NRC, 1985). Most goats can be confined with fencing 39–48 in high (Pinkerton et al., 1991), but because goats are agile climbers, the higher limit should be used when possible. Floor area requirements are 10–20 sq ft per adult animal depending on how many goats are housed together (NRC, 1985). Goats have been easily maintained at this institution in stainless steel indoor runs with raised, vinyl coated, expanded metal flooring. Ten to fifteen room air changes per hour provide adequate ventilation for goats housed indoors (NRC, 1985). A diurnal cycle of light and dark is required (Consortium for Developing a Guide, 1988).

If an outside exercise lot is used, 25 sq ft per animal should be provided (Appleman, 1984). Animals maintained in pastures or lots should have access to shade and protection from wind and rain. Hutches with three sides and a roof provide adequate shelter from wind and rain. Attention should be paid to the position of the hutches in relation to sun, wind direction, and season. While hutches can be designed with no floor and placed directly on the ground, goats seem to prefer a solid or slotted floor raised above the ground. Feces and excess hay and feed must be removed from inside and around the hutches daily. Hutches should be designed so that they can be easily moved to another location in the pas-

ture when the area around hutches becomes wet, muddy, or soiled or to allow repositioning when seasonal conditions change. Since dominant animals may push others out, the number and size of the hutches should be evaluated to ensure adequate space relative to social structure.

Feed troughs should be easy to clean and constructed so that animals cannot walk and defecate in the feed source (Pinkerton et al., 1991). There should be enough feeder space and preferably several feeders to prevent animals from dominating feed and water supplies (Consortium for Developing a Guide, 1988). Adequate feed space per adult animal is considered to be 12–20 inches (NRC, 1985). Hay should be offered in bunks or racks to prevent soiling. Reaching or climbing to pull hay down from overhead racks simulates goats' natural foraging behavior, which generally comprises from 40 to 60 percent of daily activity (Pinkerton et al., 1991). Bedding material made up of dry straw, wood shavings, or ground corn cob may be used to absorb moisture in pens (Appleman, 1984).

Nutritional needs for goats are described in the booklet, *Nutrient Requirements of Goats* (NRC, 1981). Goats are selective browsers of grasses, weeds, twigs, and sprouts; they do not like dusty or finely ground feed or musty, dusty, or moldy hay. They will not eat from a feeder contaminated by urine or feces and often will not eat hay or feed if it has dropped on the floor. Though not essential, goats prefer a variety of food and providing several forages or a mixture of grasses and legumes may aid to enrich the animal's environment (Adams, 1986; Hall, 1976). Good quality hay should be freely available. Concentrate offered to goats should amount to 0.5–1.5 lb per adult goat per day. Concentrate protein should be increased (12–14 percent) when grass hay is fed and decreased (10–12 percent) with legume hays or pasture (Pinkerton, undated). For maintenance, goats consume about 1–1.5 percent of total body weight daily (Donoghue and Kronfeld, 1990). As mentioned earlier, strict attention should be given to the ratio of calcium to phosphorus in the diet. A Ca:P ratio of less than 1.5:1 predisposes the goats to urinary calculi formation (Pinkerton et al., 1991). Ideally, the Ca:P ratio should approximate 1.75:1 (Adams, 1986) to 2:1–2.5:1 (Smith and Sherman, 1994, p.402). Laboratory diets formulated specifically for goats are available.

More than other species, goats are reluctant to drink any water that is stagnant or fouled. Therefore, water assessment is important. A good source of clean water should be provided ad libitum. Fresh water is best provided by an automatic watering system, and goats can readily be trained to use a watering system with ball valves.

Toys manufactured for the purpose of alleviating boredom and stable vices for horses can be adapted for use in indoor runs housing goats. In particular, at this institution goats appear to be entertained by hanging a red, apple-shaped, apple-scented, plastic equine toy in the runs at about their eye level.

Goats enjoy reaching or climbing to browse. They are very social animals and should be housed in groups whenever possible.

ANESTHESIA AND POSTOPERATIVE CARE

Many of the practices and equipment used for anesthesia and surgery in small animal species can also be used for ruminants. Comprehensive sources providing information on anesthesia, analgesia, and surgery care are available (Benson and Thurmon, 1986; Ewing, 1990; Smith and Sherman, 1994, pp. 509–517; Taylor, 1991; Thurmon and Benson, 1986). Individuals responsible for animals used in research and teaching should consult the guidelines created by the Council on Research of the American Veterinary Medical Association, which cover the major components associated with conducting surgery in research or teaching settings (Brown et al., 1993).

Even though many of the commonly used anesthetics, analgesics, and sedative drugs used for goats do not carry a product license specifically for goats, those listed in this manuscript have been widely tested in clinical and experimental settings (Ewing, 1990; Smith and Sherman, 1994, pp. 509–517; Taylor, 1991). Specific anesthetic regimens should be devised in consultation with the attending veterinarian taking into consideration the objectives of the protocol. The following section will outline anesthetic problems not encountered in simple-stomached animals and review commonly used protocols for small ruminant anesthesia and analgesia.

Prior to using any anesthetic protocol, a thorough physical should be performed with special attention given to the respiratory system. Supportive therapy during anesthesia should include fluids injected intravenously for maintenance and replacement needs and a source of warmth and oxygen. Fluid maintenance can be achieved with a flow rate of 4 ml/kg/hr through an intravenous catheter placed in the jugular or cephalic vein. Anesthesia is monitored in much the same way as for other species. The animal's response to surgery and vital signs reflecting the stability of the cardiac and respiratory systems should be assessed. Eye position is not considered to be a reliable indicator of the depth of anesthesia (Ewing,1990; Taylor, 1991).

The most common complications encountered with anesthetizing ruminants are associated with the effects of the digestive tract on the respiratory system. These include regurgitation and aspiration, bloat, and inadequate oxygenation (Ewing, 1990; Hellyer, 1991; Taylor, 1991; Thurmon and Benson, 1986).

Active regurgitation during light planes of anesthesia or passive regurgitation under deep anesthesia may lead to aspiration of rumen contents causing asphyxiation or progressive foreign body pneumonia. Although there will not be a significant decrease in ruminal contents, withholding food for 12 to 24 hour may decrease ruminal pressure and decrease the risk of regurgitation (Muir et. al., 1989). This may also decrease the rate of fermentation and gas production in the rumen thereby decreasing the risk of bloat (Thurmon and Benson, 1986). Fasting is not recommended for neonatal or pregnant goats, and water should not be withheld prior to anesthesia.

To help prevent aspiration of rumen contents, endotracheal intubation is recommended. While the animal is in a state of fairly deep anesthesia, quickly intubate the goat using a cuffed endotracheal tube while the animal is positioned in sternal recumbency. The cuff of the endotracheal tube should be inflated as soon as the tube is properly positioned. Due to the long, narrow oral cavity and distant laryngeal opening, an otherwise difficult intubation may be facilitated by using a laryngoscope with a long blade in order to more clearly see the position of the tube, as well as a stylet inserted into the endotracheal tube for easier placement and guidance of the tube (Ewing, 1990; Taylor, 1991; Thurmon and Benson, 1986).

Normal eructation in the goat is prevented by anesthesia and by dorsal or lateral recumbent positioning. As a result, gas increases in the rumen causing ruminal tympany or bloat, and rumen contents put pressure on the diaphragm causing the lung capacity to decrease and interfere with ventilation. Pressure on the major vessels then impedes venous flow returning to the heart. Cardiac output, blood pressure, and tissue perfusion are compromised and can lead to possible pulmonary and ventilation perfusion mismatch. Hypoxemia and hypercarbia may result and can be life threatening (Ewing, 1990; Taylor, 1991; Thurmon and Benson, 1986). Passing a stomach tube after intubation can help resolve gaseous distension. An equine uterine flushing catheter made of silicon rubber with a relatively large inflatable balloon at the distal end will facilitate placement of the tube into the gas pocket. The use of this type of tube also reduces drainage of ruminal contents and blockage of the tube (Vogler et al., 1992). Intermittent positive pressure ventilation throughout the course of anesthesia helps to prevent hypercarbia and to maintain a constant plane of anesthesia. At least 30 percent inspired oxygen should be provided for all anesthetic procedures lasting longer than 10 minutes (Taylor, 1991). Allow seven to ten breaths per minute and tidal volume of at least 10 ml/kg. If administered by hand bagging, the tidal volume should be adequate enough to cause chest expansion without exceeding 30 cm water pressure (Ewing, 1990).

The animal must be supervised until it is completely recovered. The same precautions taken to prevent the consequences of regurgitation (such as aspiration), ruminal distension, and inadequate oxygenation should be followed. If using an inhalant anesthetic, turn off the vaporizer and flush the rebreathing system with oxygen. Leave the animal connected to the system until it shows signs of recovery such as an active palpebral reflex, limb movement, chewing, and swallowing. When strong swallowing reflexes are evident, remove the endotracheal tube with the cuff inflated in order to remove any accumulated saliva or regurgitant near the cuff. The animal should be supported throughout recovery in sternal recumbency until able to maintain this position on its own (Taylor, 1991; Thurmon and Benson, 1986).

ANESTHETICS AND PREMEDICATIONS

Sedatives may be used as premedications or in conjunction with regional anesthesia for certain procedures (Taylor, 1991). Premedications using sedatives help make catheterization easier and induction smoother by minimizing stress and anxiety (Dr. Peter Hellyer, Personal Communication, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina).

While acepromazine (0.05–0.1 mg/kg IV) (Smith, 1994) provides mild sedation, it is not considered that useful in goats (Hellyer, 1991). A total dose of 3 mg of acepromazine should not be exceeded.

Xylazine (0.1–0.2 mg/kg IM), an alpha-2-agonist, may be used as a premedication. The low concentration (20 mg/ml) formulation should be used. Ruminants are more sensitive to the effects of xylazine than are most other species. Xylazine causes cardiovascular and respiratory depression, rumen atony with bloat, hyperglycemia with resultant diuresis, and abortions in late gestation (Thurmon and Benson, 1986). Xylazine should not be used for animals with depressed cardiovascular function or urinary tract obstruction.

Diazepam (0.25–0.5 mg/kg IV) is useful in providing sedation without analgesia in goats when slowly given intravenously (Taylor, 1991).

Ketamine and xylazine are usually used together as a preanesthetic to permit the intubation of the animal before using inhalation anesthetics. Xylazine (0.05 mg/kg) is given

intravenously and ketamine (2 mg/kg IV) is given three to five minutes later. The intravenous dose of ketamine may be repeated if needed (Ewing, 1990).

Diazepam may be substituted for the xylazine in combination with ketamine when xylazine is contraindicated. A premedication dose of diazepam (0.5 mg/kg or one half this dose if the animal is over 50 kg) is slowly injected intravenously. Ketamine (2 mg/kg IV) should be given about three minutes later (Ewing, 1990).

For a longer affect, administration of xylazine (0.22 mg/kg) and ketamine (11 mg/kg) IM in combination will give approximately 50 minutes of anesthesia. A prolonged recovery time of 1.5 to 2 hours is usual (Ewing,1990). A review of the references previously cited will reveal other ketamine/xylazine/diazepam "cocktails" that are used for goats. Some of these incorporate opioids into the protocol for additional analgesic effects.

Ultrashort acting barbiturates are often employed as induction agents. Thiamylal (8–14 mg/kg IV) or thiopental (10–16 mg/kg IV) allow intubation prior to inhalation anesthesia (Ewing,1990). These doses may be decreased if using a premedication sedative (Dr. Peter Hellyer, Personal Communication, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina).

Mask induction can be achieved using halothane or isoflurane in oxygen. Initially, the goat should be allowed to breathe 100 percent oxygen at a flow rate of 4 to 6 L/min for several minutes to achieve denitrification. The inhalant should be slowly increased by 0.5 percent increments every 30 seconds until a 3 to 3.5 percent vaporizer setting is reached. Intubation is likely to be possible in 10 minutes (Ewing, 1990). Oxygen flow rate can be decreased to 1 to 2 L/min and the vaporizer setting can be maintained at a level of 0.5–2 percent for halothane and 1–2 percent for isoflurane. Oxygen flow rate can be calculated by the following formula: 3–5 ml/lb body weight × 5 = oxygen flow rate in L/min (Dr. Frankee P. Elliot, Personal Communication, Department of Medicine and Surgery, Veterinary Teaching Hospital, University of Missouri, Columbia, Missouri). Proper precautions should be undertaken to reduce human exposure to extraneous gasses by ensuring that a tight-fitting mask and a proper scavenging system are used during inhalation anesthesia.

Local and regional analgesics are often appropriate for certain procedures including orthopedic surgeries. Landmarks and procedures are detailed elsewhere (Benson and Thurmon, 1986). A total dose of 2 percent lidocaine should not exceed 15 ml in any goat. Administration of diazepam as an anticonvulsant and proper ventilation support must be administered should complications arise (Benson and Thurmon, 1986).

PAIN RECOGNITION AND RELIEF

Postsurgical evaluation of the animal should include close monitoring for overt and subtle signs of pain. Presurgical parameters including respiratory rate, heart rate, amount of vocalization and activity, and general appearance and attitude should be recorded to be used as a basis for postsurgical evaluation. Increased heart rate, rapid shallow respirations, grunting and grinding teeth might be indications of pain, and a depressed appetite, guarding of affected area, vocalization on movement or palpation, and other changes in behavior are further evidence that an animal is in pain (Benson, 1992). A goat might also appear depressed and disinterested in its surroundings.

The opioids are a class of analgesics often employed as preoperative and postoperative analgesics. Meperidine (10 mg/kg) may be used as a premedication (Ewing, 1990). Buprenorphine (0.005–0.01 mg/kg), a more recently introduced opioid, may have a longer duration of action than others in its class. Although the recommended dosing interval for most species is 6–12 hours, buprenorphine has a shorter duration of action in ruminants and should be given every 4 to 6 hours (Flecknell, 1989; Fujimoto, 1992). Standard procedure at Clemson University is to incorporate buprenorphine (0.005 mg/kg) as a premedication. It is then dosed at 0.005 to 0.01 mg/kg every 4–6 hr. In our experience, this protocol has provided excellent postoperative analgesia in most cases.

Nonsteroidal anti-inflammatory agents such as flunixin meglumine (1.1 mg/kg) may be incorporated into a postsurgical analgesic protocol especially those involving the musculoskeletal system. This should be dosed as needed every 12–24 hours but not to exceed 2–4 doses. Higher repeated doses can cause hemorrhagic gastritis (Paddleford, 1992).

Appropriate sites for subcutaneous injections are the neck (Williams, 1990), flank, and axillary area. Intramuscular injections should use the neck, triceps, and quadriceps muscles in order to prevent temporary or permanent lameness associated with ischiatic nerve irritation. The subcutaneous route for injections is preferable over the intramuscular route and should be used whenever possible. The jugular or cephalic veins are accessible for intravenous injections (Ewing, 1990).

CONCLUSION

Goats are becoming an important laboratory animal model in many fields of biomedical research and teaching. As other large animal models are becoming more costly and difficult to procure, the research community must search for suitable alternatives. Often existing runs, kennels, and transport cages designed for other larger traditional laboratory animals (such as dogs and swine) can be easily modified for goats. Dairy goat operations are a potential source of quality research animals. Many of these dairy operations practice good management and health programs, and they routinely produce excess male animals for which there is little market. The friendly and docile nature of the goat make it a desirable animal model for research and teaching programs.

An overview of general husbandry practices, dietary and

health concerns, unique considerations for anesthesia in goats, and applications as research models have been described in this article. References provided should be reviewed for more comprehensive information in each area.

REFERENCES

Adams, R. S. 1986. Dietary management in goats. Pp 264-271 in Current Veterinary Therapy 2: Food Animal Practice, J. L. Howard, ed. Philadelphia: W. B. Saunders.

Consortium for Developing a Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching. 1988. Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching. Champaign, Ill.: Association Headquarters. (Available at a cost of $5.00 each from Association Headquarters, 309 West Clark Street, Champaign, Illinois 61820. Tel: 1-217-356-3182).

Appleman, R. D. 1984. Housing. Pp B-1:1-3 in Extension Goat Handbook, G. F. W. Haenlein and D. L. Ace, eds. Newark, Del: Cooperative Extension Service, University of Delaware.

Ayers, J. L. 1984. Enterotoxemia. Pp G-10:1-2 in Extension Goat Handbook, G. F. W. Haenlein and D. L. Ace, eds. Newark, Del: Cooperative Extension Service, University of Delaware.

Basnur, P., and Yodaul, B. 1990. Genetic diseases of sheep and goats. Pp. 779-802 in Veterinary Clinics of North America: Food Animal Practice, Vol. (6)3, M. Smith, ed. Philadelphia: W. B. Saunders.

Benson, G. J. 1992. Defining Pain in Laboratory Animals. Nashville, Tenn.: Office for Protection from Research Risks, Vanderbilt University Medical Center, and Maharry Medical College Workshop on Minimizing Pain and Distress in Laboratory Animals.

Benson, G. J., and J. C. Thurmon. 1986. Regional analgesia of food animals. Pp 71-83 in Current Veterinary Therapy 2: Food Animal Practice, J. L. Howard, ed. Philadelphia: W. B. Saunders.

Blackwell, T. E. 1983. Enteritis and diarrhea. Pp. 557-570 in Veterinary Clinics of North America: Large Animal Practice, Vol. 5(3), M. Smith, ed. Philadelphia: W. B. Saunders.

Bliss, E. L., E. A. Oltenacu, and R. S. Ott. 1984. Reproductive management. Pp D-6:1-3 in Extension Goat Handbook, G. F. W. Haenlein and D. L. Ace, eds. Newark, Del: Cooperative Extension Service, University of Delaware.

Bliss, E. L. 1984. Herd health program. Pp G-1:1-3 in Extension Goat Handbook, G. F. W. Haenlein and D. L. Ace, eds. Newark, Del: Cooperative Extension Service, University of Delaware.

Brown, M. J., P. T. Pearson, and F. N. Tomson. 1993. Special report: Guidelines for animal surgery in research and teaching. Am. J. Vet. Res. 54(9):1544-1559.

Bulgin, M. S. 1990. Ovine progressive pneumonia, caprine arthritis encephalitis and related lentiviral diseases of sheep and goats. Pp. 691-704 in Veterinary Clinics of North America: Food Animal Practice, Volume 13, M. Smith, ed. Philadelphia: W. B. Saunders.

Burrows, C. F. 1994. A closer look—cryptosporidium. Perspect. Resource Women Vet. Med. July/August 1994:53-54.

Crandell, R. A. 1986. Contagious ecthyma. Pp. 515-517 in Current Veterinary Therapy 2: Food Animal Practice. Philadelphia: W. B. Saunders.

Donoghue, S., and D. Kronfeld. 1990. Clinical nutrition of sheep and goats. Pp. 563-576 in Veterinary Clinics of North America: Food Animal Practice, Volume 6(3), M. Smith, ed. Philadelphia: W. B. Saunders.

Ebert, K. M. 1993. Transgenic farm animals: Progress report. Theriogenol. 39(1):121-135.

Ewing, K. K. 1990. Anesthesia techniques in sheep and goats. Pp. 759-778 in Veterinary Clinics of North America: Food Animal Practice, Volume 6(3), M. Smith, ed. Philadelphia: W. B. Saunders.

Flecknell, P. A. 1989. Rodent and Rabbit Anesthesia Lecture. Presented at 40th Annual American Association for Laboratory Animal Science Meeting. Little Rock, Ark.

Foreyt, W. J. 1990. Coccidiosis and cryptosporidiosis in sheep and goats. Pp. 655-670 in Veterinary Clinics of North America: Food Animal Practice, Volume 6(3) M. Smith, ed. Philadelphia: W. B. Saunders.

Freeman, W. A. 1992. Goat Health. Presented at annual American Veterinary Medical Association meeting. Boston, Mass.

Fubini, S. L., and S. G. Campbell. 1983. External lumps on sheep and goats. Pp. 457-476 in The Veterinary Clinics of North America: Large Animal Practice, Volume 5(3), M. Smith, ed. Philadelphia: W. B. Saunders.

Fujimoto, J. L. 1992. Dosage tables for opiate agonist and agonist-antagonists in laboratory animals. Pp. 539-542 in Animal Pain, Charles E. Short and Alan Vam Poznak, eds. New York: Churchill Livingstone.

Guss, S. B., and D. L. Ace. 1984. Economics of dairy goats. P. A-4:1 in Extension Goat Handbook, G. F. W. Haenlein and D. L. Ace, eds. Newark, Del: Cooperative Extension Service, University of Delaware.

Hall, Richard. 1976. Do you have a goat? Current Information Series No. 352: October, 1976, University of Idaho College of Agriculture: Cooperative Extension Service Agricultural Experiment Station.

Hellyer, P. 1991. Anesthesia in Small Ruminants. Lecture presented at Clemson University, Clemson, S.C.

Lincicome, P. P., and A. Hall. 1984. The pygmy. Pp. B-7: 1-4 in Extension Goat Handbook, George F. W. Haenlein and Donald L. Ace, eds. Newark, Delaware: Cooperative Extension Service, University of Delaware.

Muir, W. W., J. A. E. Hubbell, and R. Skarda. 1989. Pp. 220-227 in Handbook of Veterinary Anesthesia. St. Louis: C. V. Mosby Company.

National Research Council (NRC). 1985. Guide for the Care and Use of Laboratory Animals. Washington, D.C.: U.S. Department of Health and Human Services (Available from the Office for Protection from Research Risks, Division of Animal Welfare, National Institutes of Health, 6100 Executive Blvd., MSC 7507, Rockville, MD 20892-7507. Tel: 301-496-7163; Fax: 301-496-2803).

National Research Council (NRC). 1981. Nutrient Requirement of Goats. Washington, D.C.: National Academy Press.

Nelson, D. R. 1984. Metabolic and nutritional diseases. Pp. C-5:1-3 in Extension Goat Handbook, G. F. W. Haenlein and D. L. Ace, eds. Newark, Del: Cooperative Extension Service, University of Delaware.

Paddleford, R. R. 1992. Post-operative pain control and chronic pain management in primates, small ruminants, and swine. Office for Protection from Research Risks, Vanderbilt University Medical Center, and Meharry Medical College Workshop on Minimizing Pain and Distress in Laboratory Animals. Nashville, Tenn.

Phelps, S. L., and M. Smith. 1993. Caprine arthritis-encephalitis virus infection. J. Am. Vet. Med. Assoc. 203(12):1663-1666.

Pinkerton, F. Undated. Feeding Practices for Dairy Goats. Langston, Okla.: American Institute for Goat Research, Langston University.

Pinkerton, F., D. Scarfe, and B. Pinkerton. 1991. Meat goat production and marketing—fact sheet M-01. Langston, Okla: de la Garza Institute of Goat Research.

Rexroad, C. E. 1994. Transgenic farm animals. ILAR News. 36(1):5-9.

Robinson, R. A. 1983. Respiratory disease of sheep and goats. Pp. 539-555 in Veterinary Clinics of North America: Large Animal Practice, Volume 5(3), M. Smith, ed. Philadelphia: W. B. Saunders.

Sherman, D. M. 1989. Johne's disease. Pp. G-12: 1-3 in Extension Goat Handbook, G. F. W. Haenlein and D. L. Ace, eds. Newark, Del.: Cooperative Extension Service, University of Delaware.

Simecka, J. W., Davis, M. K., S. E. Ross, C. T. K. -H. Stadtländer, and G. H. Cassell. 1992. Mycoplasma diseases of animals. Pp. 391-415 in Mycoplasmas—Molecular Biology and Pathogenesis, J. Maniloff, R. N. McElhaney, L. R. Finch, and J. B. Baseman, eds. Washington, D.C.: American Society for Microbiology.

Singh, S. B., and C. M. Lang. 1985. Q-fever serologic surveillance program for sheep and goats at a research animal facility. Am. J. Vet. Res. 46:321-325.

Sinn, R. 1992. Introduction. Pp. 1-9 in Raising Goats for Milk and Meat. Little Rock, Ark.: Heifer Project International.

Smith, M. C. 1983. Foot problems in goats. Pp. 489-490 in The Veterinary Clinics of North America, Volume 5(3), M. C. Smith, ed. Philadelphia: W. B. Saunders.

Smith, M. C. 1984. Coccidiosis. Pp G-6: 1-3 in Extension Goat Handbook,

G. F. W. Haenlein and D. L. Ace, eds. Newark, Del.: Cooperative Extension Services, University of Delaware.
Smith, M. C. 1990. Exclusion of infectious diseases from sheep and goat farms. Pp. 705-720 in Veterinary Clinics of North America: Food Animal Practice, Volume 6(3), M. Smith, ed. Philadelphia: W. B. Saunders.
Smith, M. C., and D. Sherman. 1994. Goat Medicine. Philadelphia: Lea and Febiger.
Sponenberg, D. P. 1993. Sheep and Goat Breed Resources in (or Available to) the USA. In Proceedings of the 1993 Symposium on the Health and Disease of Small Ruminant Practitioners. Ithaca, NY.
Taylor, P. 1991. Anesthesia in sheep and goats. In Practice, Jan 91:31-36.
Tenorio, E., R. Ermal, S. Giri, and D. Brooks. 1992. Caprine arthritis encephalitis virus (CAEV) infection in goats as a model for rheumatoid arthritis. Lab Animal 21(1):33-36.
Thurmon, J. C., and G. J. Benson. 1986. Anesthesia in ruminants and swine. Pp. 51-71 in Current Veterinary Therapy 2: Food Animal Practice, J. L. Howard, ed. Philadelphia: W. B. Saunders.
Vogler, G. A., W. A. Morgenthaler, P. A. Frank, and L. J. Baudendistoe. 1992. Control of tympany and salivation during anesthesia of small ruminants. Contemp. Top. 31(2):24-25.
Williams, C. S. F. 1984. Disease management. Pp. G-3: 103 in Extension Goat Handbook, G. F. W. Haenlein and D. L. Ace, eds. Newark, Del.: Cooperative Extension Service, University of Delaware.
Williams, C. S. F. 1990. Routine sheep and goat procedures. Pp. 737-758 in Veterinary Clinics of North America: Food Animal Practice, Volume 6(3), M. Smith, ed. Philadelphia: W. B. Saunders.

Issues for Institutional Animal Care and Use Committees (IACUCs)

Integrating Agricultural and Biomedical Research Policies: Conflicts and Opportunities

Philip Tillman

OVERVIEW: BIOMEDICAL AND AGRICULTURAL USES OF FARM ANIMALS

Research facilities use farm animals in several ways. They may be used as "animal models," in which case the subject species is studied with the intention of applying the knowledge to human beings (or sometimes to another animal species). Farm animals may also be studied for their intrinsic interest to gain fundamental knowledge about animal biology. Chickens might be used to study animal behavior or avian evolution, which may have potential application in better characterizing animal models or the genetic components of a disease. These sorts of studies may be referred to as "biomedical" studies. Farm animals are also studied with the intention of applying the knowledge gained to the efficient production of food and fiber by the subject species. Such studies are clearly "agricultural" in nature. Agricultural studies are fundamental to the production agriculture departments of U.S. Land Grant Colleges.

Farm animals may also be used in ways that cross the boundary between biomedical and agricultural studies. For example, the agricultural production colonies of an institution may supply animals (or embryonated eggs) for biomedical research. A study may be collaborative between an agricultural scientist and a biomedical scientist—each employing the same procedures, but interested in the data for different reasons. A physiologist may be interested in the effects of a new beta adrenergic agonist because of its potential relevance to human physiology, while an animal scientist might be interested in the same data because of its relevance to meat production. In many cases, it isn't easy to categorize a particular project as biomedical or agricultural. The distinction becomes less and less clear as biochemists, physiologists, and biomedical engineers become more and more prevalent within our agricultural universities.

The sometimes "fuzzy" border between agricultural and nonagricultural studies has become a topic of great interest to university Institutional Animal Care and Use Committees (IACUCs). In 1990, the U.S. Department of Agriculture (USDA) announced its intention to draft standards for the use of farm animals in biomedical research (Federal Register, Vol. 55, No. 66, p. 12667, April 5, 1990). USDA animal welfare inspectors now visit research institutions and ask if particular animals are being used for biomedical or agricultural research. If the study is biomedical, the research project and the husbandry procedures under which the animal is maintained are matters of federal regulation.

Institutions conducting both agricultural and biomedical research must sooner or later decide what role, if any, the IACUC will play in the oversight of agricultural studies. If the IACUC is to play a role in the governance of agricultural studies, then it will have to determine what standards are applicable to agricultural studies.

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REGULATORY REQUIREMENTS AND INSTITUTIONAL DECISIONS

In general, agricultural production studies in farm animals have been specifically excluded from the regulations and guidelines requiring IACUC oversight of animal research. The Federal Animal Welfare Act regulations specifically exempt "horses not used for research purposes and other farm animals, such as, but not limited to livestock or poultry, used or intended for use as food or fiber, or livestock or poultry used or intended for improving animal nutrition, breeding, management, or production efficiency, or for improving the quality of food or fiber" (9 CFR 1.1). The Health Research Extension Act (42 USC 289d) was amended November 20, 1985 by Public Law 99-158 to cover the care and use of animals in research. This law applies to all live vertebrate species, but only when they are used in Public Health Service (PHS) funded activities. Numerous other federal and private agencies require IACUC review of funding proposals and adherence to the principles provided in the *Guide for the Care and Use of Laboratory Animals* (*NIH Guide*) (NRC, 1985; FDA, 1992; NSF, 1985), but in general these agencies do not fund agricultural research.

It is much less common for an agricultural funding entity to require IACUC review of submissions, although USDA's Cooperative State Research Service does require IACUC review of the agricultural production studies that it funds. Apart from the requirements of specific funding agencies, there is no legal requirement for any sort of oversight or review of purely agricultural studies.

An institution could choose to exclude all its agricultural units from IACUC review without violating any law or regulation. An institution could also develop an alternate means of oversight, perhaps a separate committee, for agricultural production facilities and studies. The *Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching* (*Ag Guide*) recommends committee oversight of agricultural studies, and discusses the possibility of a separate committee for review of agricultural activities (Consortium for Developing a Guide, 1988).

If an institution decides to monitor the care and use of animals in agricultural research, either through the IACUC or another mechanism, the institution must then decide what standard should be used to evaluate agricultural studies and husbandry methods.

Figure 1 (options for the oversight of agricultural animals in research) shows the cascade of decisions that determine what role the IACUC will have in the oversight of studies involving farm animals. Note that there are two entirely voluntary policy decisions that fall to the administration of the institution: (1) Should one IACUC have oversight over both agricultural studies and biomedical studies? and (2) Should the same standards be applied to agricultural and biomedical studies?

ONE IACUC OR TWO?

An institution might choose to appoint separate IACUCs for agricultural and nonagricultural studies. The arguments in either direction might be presented as follows:

An agriculture IACUC (Ag-IACUC) would be staffed largely by scientists with expertise in production agriculture. An Ag-IACUC might be seen as more credible and authoritative to an agricultural faculty than an IACUC composed largely of physicians, for example. Agricultural scientists would have greater knowledge of conditions in the agricultural industry, which might have to be modeled in research projects. Finally, in many instances, agricultural scientists might have greater knowledge of the particular species under study.

A disadvantage of a dual IACUC system would be its tendency to divide and fragment the institution rather than build consensus and uniformity. One might find that a given procedure could be approved in one department and not in another. One would have to establish policy which would determine to which committee a particular type of study should be submitted. Would the two IACUCs' areas of authority be based on the species under study, the academic department of the scientist, or the nature of the study? If the study had both agricultural and nonagricultural significance, which committee would have authority?

A single IACUC, representing both biomedical and agricultural scientists, also has its advantages. The single IACUC would represent the whole of, rather than a subunit of the institution. A single, broadly constituted IACUC could establish guidelines and policies that could apply across academic lines in an unbiased way. If the IACUC had to investigate and act on a complaint expressed by the general public, a broadly constituted IACUC might be seen as less biased than an IACUC more directly connected with a particular research group or department.

ONE POLICY, TWO, OR THREE?

After determining whether or not agricultural studies and nonagricultural studies should be reviewed by the same committee, the institution must then determine what standards are to be used in reviewing protocols and inspecting vivaria. The majority of governmental and private funding sources have used the *NIH Guide* for this purpose. The upcoming USDA standards for farm animals will apply to farm animals used in biomedical studies, but not to those used in agricultural studies. USDA was directed by congress to confer with the Department of Health and Human Services in drafting standards under the Animal Welfare Act, with the intent of establishing uniformity of standards between the two agencies.

In drafting new regulations, USDA is expected to make extensive use of existing documents, such as the *NIH Guide* and the *Ag Guide*. It remains to be seen which document will have greater influence on USDA's proposed rules. The *Ag Guide* has been widely advocated for use as a primary source

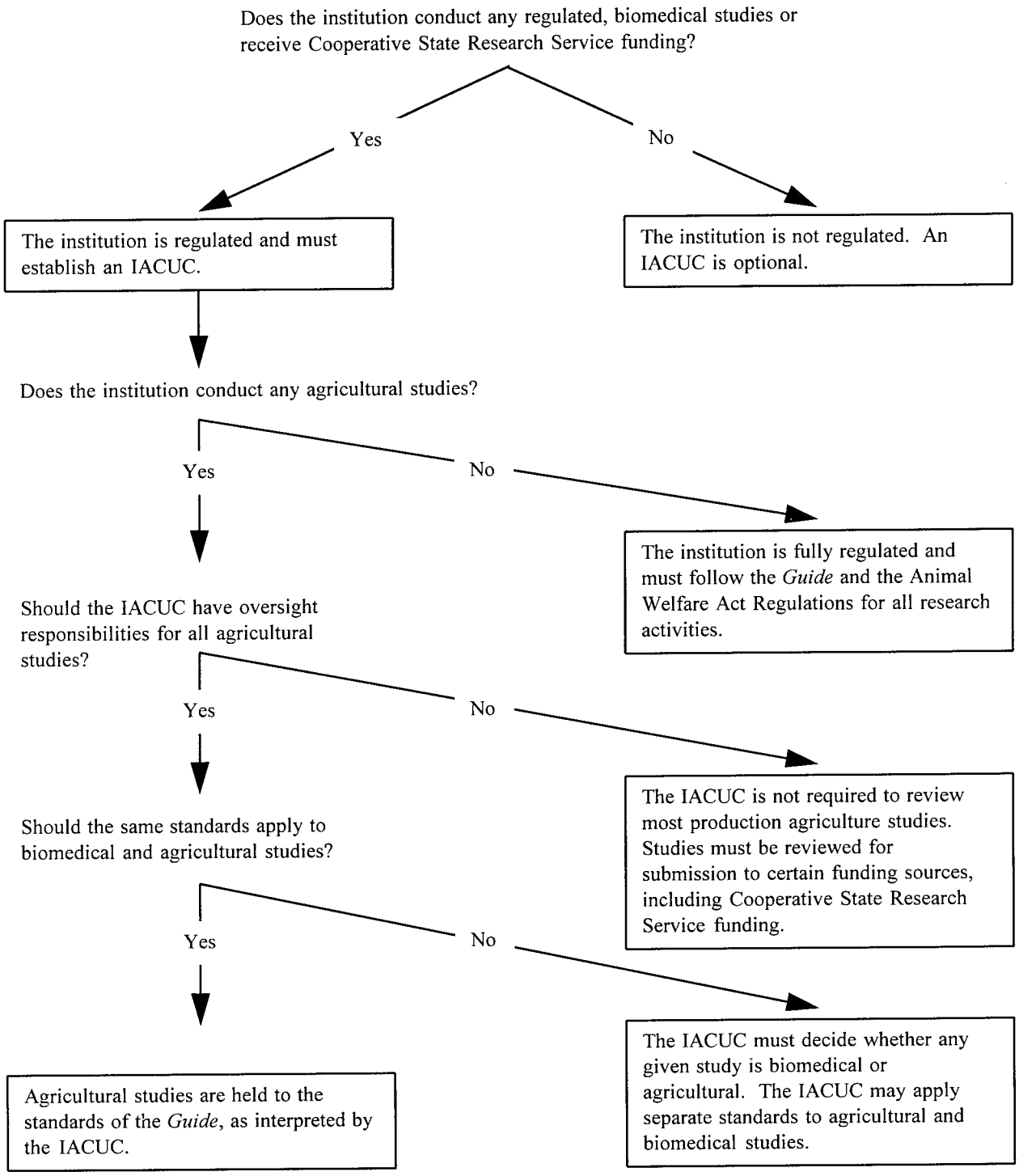

FIGURE 1 Decision tree: options for the oversight of agricultural animals in research.

document for the USDA regulations. Many researchers have praised the *Ag Guide* for its greater flexibility and more extensive discussions of agricultural practices.

There would be, however, potential conflict inherent in using the *Ag Guide* as the primary source document in lieu of the *NIH Guide*. The *NIH Guide* deals only with biomedical research, not with agricultural production research. USDA's farm animal standards will clearly regulate the biomedical studies for which the *NIH Guide* was written. USDA's regulations will clearly *not* regulate the studies for which the *Ag Guide* was written, since agricultural production studies fall outside USDA's jurisdiction. Ideally, USDA's regulations will draw from the best of each of these source documents, but they must adhere closely enough to the *NIH Guide* to avoid producing conflicting regulations for biomedical studies.

For agricultural production studies, there are a variety

of other source documents, the most widely recognized of which is the *Ag Guide*. Those portions of the *Ag Guide* dealing with animal husbandry have been adopted by the American Association for Accreditation of Laboratory Animal Care (AAALAC) as an applicable standard for agricultural studies. AAALAC provides further guidance in a policy statement on farm animal facilities, which states, ". . . housing and care for farm animals should meet the standards that prevail on a high-quality, well-managed farm. These standards are those promulgated by state agricultural extension services and the land-grant universities" (AAALAC, 1991).

A single IACUC could review each facility and project and apply the most appropriate standards or guidelines (whether USDA Animal Welfare Regulations, the *NIH Guide*, or the *Ag Guide*). They could also use AAALAC's policy statement as a guideline and employ a community standard, by asking for each protocol, "Does this facility or study represent the standards of a high-quality, well-managed farm in our state?"

Of the various documents that might be used as standards, the *NIH Guide* is the most demanding. The cage sizes are often the largest, the requirements for sanitation are the most stringent, the climate control requirements the most exacting, and the programmatic requirements the most specific. A strong argument could be made that an institution establishing policy for animals should adopt the *NIH Guide* as the single standard. If the requirements for the *NIH Guide* are met uniformly throughout a campus, then every animal facility and every animal activity is fully qualified to seek funding from any granting agency. Adopting a dual standard might limit sources of funding to particular departments or particular animal facilities.

The *NIH Guide* states specifically that it does not deal with the use of farm animals in research intended for production agriculture (NRC, 1985, p. 2). However, it is a very flexible document, laying out general principles of animal care more frequently than it specifies particulars. For example, under "Food" the *NIH Guide* states, "Animals should be fed palatable, uncontaminated, and nutritionally adequate food daily or according to their particular requirements, unless the experimental protocol requires otherwise" (NRC, 1985, p. 22). There would be no difficulty applying this guideline to the care of animals in biomedical research, agricultural research, production agriculture, zoological parks, as well as to pet care.

The *NIH Guide* also clearly states, "*Professional judgement is essential in the interpretation of these guidelines*" (emphasis in original) (NRC, 1985, p. 2). The *NIH Guide* invites the reader to consider not only the specifics, but the rationale behind them, and allows the freedom to vary from the specifics of the *NIH Guide* when good reason can be given. For example, if a study must model conditions of a farm in order to be scientifically valid, it would not be in conflict with the *NIH Guide* to allow the use of commercial agricultural caging.

STANDARDS, DOUBLE STANDARDS, AND GUIDELINES

Given that it would fall within an IACUC's authority to apply agricultural standards to agricultural projects, how great a difference should the IACUC expect to observe between agricultural facilities and nonagricultural facilities? What will the differences be? What sorts of Judgements of Solomon will be required of the IACUC? A few examples of the more obvious differences between contemporary biomedical standards and agricultural standards are given below.

Space requirements

It's difficult to make direct comparisons between the space requirements of the *NIH Guide* and those of the *Ag Guide*. Each source gives space requirements in tabular formats, but the types of housing listed and the categories of animals often are not directly comparable. The differences between the two documents are often minimal, especially for the species, housing types, and weight ranges commonly used in biomedical studies*. Consider the examples of space requirements as given in the *NIH Guide* and the *Ag Guide* (Table 1).

Sanitation Practices

Sanitation practices are very different between biomedical and agricultural facilities. For example, the *NIH Guide* requires that wire bottom cages be washed at least every 2 weeks. Wire bottom poultry cages in agricultural facilities might only be sanitized between successive groups of animals; perhaps at intervals of several months. Even in the case of ruminants, swine, and horses, disinfection of a primary enclosure is the exception rather than the rule. Most frequently, waste is simply removed, with disinfection reserved for periods when the enclosure is emptied between successive lots of animals.

Force Molting

Chickens used for egg production lay eggs for a period of months and then stop. They may be induced to molt and resume laying by a variety of techniques collectively known as "force molting." Several variants of force molting techniques have been developed by the Experiment Stations and agricultural faculty of land grant universities. All methods involve stress induction by deprivation of food or water. In

*Since USDA has not yet published its standards for farm animals in Animal Welfare Act regulated research, comparisons with other standards are not possible. It is likely that USDA's standards will be similar to the *Guide*. In the conference report for the 1985 amendments to the Animal Welfare Act, Congress directed USDA to confer with other agencies in writing regulations. ". . . it is hoped that agencies continue an open communications to avoid conflicting regulations wherever possible or practical" (Congressional Record, 17 December 1985, Vol. 131, No. 175, Pt. II.)

TABLE 1 Space requirements in the *Guide* and the *Ag Guide*

Species/Type	Body Size	Housing Type	*Guide*	*Ag Guide*
Dry Ewes	65-90 Kg	Dirt lot		2.32-3.72 m^2
Dry Ewes	65-90 Kg	Paved lot		1.49 m^2
Sheep	> 50 Kg	1-4 per pen	1.86 m^2	
Laying Hen	Leghorn-Type	Wire Cage		387 cm^2
Chicken	> 3 Kg	Cage	285 cm^2	

the "California Program" water is provided freely, but all food is withdrawn for 10–14 days (North, 1984, pp. 341–356), during which time a small percentage of the animals may die. This agricultural practice is described in texts and in publications of Land Grant Colleges and Experiment Stations. Force molting could easily be employed on a "high quality, well-managed farm." The practice is not discussed in the *Ag Guide*.

Chickens are occasionally used in biomedical research as antibody producers, harvested from their eggs. If a valuable antibody producer comes to the end of a laying cycle, it is possible to "force molt" the chicken in order to accelerate its return to antibody production. The *NIH Guide* states that, "Animals should be fed palatable, uncontaminated, and nutritionally adequate food daily or according to their particular requirements, unless the experimental protocol requires otherwise" (NRC, 1985, p. 22). Should a biomedical investigator be allowed to force molt a chicken in order to return it to antibody production? Is a ten-day fast compatible with the *NIH Guide*? This question could easily be presented to an IACUC.

Physical Facilities

Both agricultural and biomedical housing facilities seek to provide the animals with the necessities of life and health, however, some of the premises underlying facility design are quite different. The emphasis in a biomedical facility is on environmental control. The facility seeks to eliminate all possible variation among experiments by finely controlling variables such as temperature, ventilation, and light. The *NIH Guide* suggests that temperature in an ideal animal room should be controllable within one degree centigrade. This extreme degree of climatic control is not advocated to promote the well-being of the animal as much as to control variation among experiments.

A fundamental goal of agricultural facilities is efficiency and economy. An agricultural scientist's primary goal is the efficient production of food and fiber. An agricultural facility is designed to meet the animal's minimum needs at minimum expense. Accordingly, while agricultural facilities are likely to consume less energy, they demonstrate less climatic control. They may make use of ambient air and lighting, evaporative coolers, direct misting of animals for cooling, and other economies not normally seen in biomedical facilities.

Surgical Facilities

Major operative procedures, as defined in the Animal Welfare Act regulations (9 CFR 1.1), are often performed under much less stringent conditions in commercial agriculture than in biomedical research. For example, in an agricultural setting, a bovine or ovine caesarian section would most often be performed in a procedure area of a barn. Sometimes the procedure might occur in an outdoor stanchion. It is highly unlikely that the animal would be prepared for surgery in a room other than the one in which the procedure took place. In a PHS funded biomedical study, similar procedures would require a dedicated survival surgery suite and the animal would be prepared for surgery in a room other than the operating room (NRC, 1985, p. 37). The *NIH Guide*, by its deference to professional judgement, would presumably allow the IACUC considerable latitude in determining exactly which procedures would require a dedicated surgical facility. The Animal Welfare Act regulations are likely to be more rigid.

Husbandry Procedures

In addition to the animal procedures required as a part of a particular study, there are a large number of normal agricultural practices that are incidental to the maintenance of the animals. A few of these common agricultural practices are subjects of controversy in their own right. The *Ag Guide* refers to these procedures as the "Special Category of Standard Agricultural Practices." Such practices, in addition to force molting, might include branding, dehorning, castration, tail-docking in swine, and beak-trimming in poultry. Key issues in evaluating the humaneness of these procedures would be the ages at which these procedures were performed, and whether anesthesia might be required for any these procedures.

Should the IACUC review and endorse the routine husbandry practices of the facility? Should the IACUC review the "Special Category of Standard Agricultural Procedures?" Or, should the IACUC review only the specific research proposal itself and defer to the animal care staff with respect to animal husbandry procedures? In the case of purely agricultural studies, and in the absence of any specific legislative mandate, the IACUC is not required to review such procedures. IACUCs may or may not review husbandry proto-

cols, according to the charge given by the institutional official who appoints the IACUC.

The *Ag Guide* recommends that a committee, either the IACUC or a separately designated "Ag-IACUC," review the husbandry practices of the institution. In the absence of regulation, an IACUC would have tremendous latitude in evaluating such procedures. Review by an IACUC might help to ensure that procedures employed within the institution are consistent with the sentiments of a broad range of institutional scientists and staff.

MAKING THE SHOE FIT: WHICH STUDY GOES WHERE?

Although the published standards of agricultural research are often different from those shown in the *NIH Guide*, the IACUC has tremendous latitude and may use considerable "professional judgement" as it interprets the *NIH Guide*. For example, the *NIH Guide* recommends that horses housed in pens be allotted 144 sq ft. Let us suppose that an IACUC performing a semiannual inspection found a horse stall measuring only 11 ft by 12 ft (132 sq ft). If the IACUC found that the horse had adequate freedom of movement, that the conditions in the barn were otherwise conducive to the animal's well-being, and that the animal was allotted adequate exercise, it would be entirely compatible with the *NIH Guide* for the IACUC to exert its professional judgement and find that the housing was adequate.

USDA regulations, being regulations and minimum standards rather than guidelines, are much less likely to be flexible. Accordingly, the distinction between agricultural and biomedical studies will become even more important after the USDA standards for farm animals are written.

Consider the following hypothetical projects. How would your IACUC deal with these issues?

The Chicken and the Egg. Imagine a production facility of laying chickens. All the birds are in good health. The housing is of an agricultural type. The battery-type cages are fixed in place and a given chicken remains in the same cage during all its productive life. The floor is scraped clean every week, but the cages are only sanitized every several months between successive lots of birds. Imagine that half of these chickens are involved in an agricultural production study. The other half have been sensitized with an antigen and their eggs are being collected for antibody production. The latter chickens are owned by a biomedical researcher and the study is funded by the National Institutes of Health (NIH). All the chickens appear well, and one can only distinguish between the two groups of chickens by examining their cage cards. Can the IACUC allow the chickens in the NIH study to reside in the same barn with the chickens in the agricultural study? Is it rational for the IACUC to declare the sanitation program suitable for one group of chickens and unsuitable for another?

The Genetically Engineered Cow. Two dairy cattle, both the products of genetic engineering, live under agricultural conditions in adjacent outdoor paved pens. One has been genetically engineered to produce an enzyme in its milk that improves the quality of cheese. The other has been genetically engineered to produce a human clotting cofactor in its milk. The IACUC inspects the facility and finds the "biomedical" cow's pen is too small to satisfy the space recommendations of the *NIH Guide*. The "agricultural" cow may remain where it is. Must the "biomedical" cow be moved?

USDA Policy Memoranda

Although the USDA has not yet issued standards specific to the housing of farm animals, it has already made a number of policy determinations regarding the distinctions between agricultural and biomedical activities. In an August 28, 1990 policy memorandum to USDA personnel (USDA, 1990), a deputy administrator held that facilities keeping rabbits, goats, sheep, and other farm animals as blood producers were considered research facilities only when the animals produced antibodies. If the facility uses blood donor animals for blood products only, such as complement, serum, and agar plates, then it is considered a dealer (and therefore does not need an IACUC). If the blood collection is incidental to the slaughter of the animals, then the activity is agricultural and not regulated at all.

An April 23, 1992 USDA policy memorandum (USDA, 1992a) held that the use of farm animals for teaching purposes in veterinary schools is considered "biomedical" rather than "agricultural," and therefore a regulated activity. The implication of this ruling is that when veterinary students perform major operative procedures on university owned animals as a part of teaching exercises, the procedures are regulated. The procedures must be conducted in dedicated surgical facilities, and the IACUC must review protocols for these activities, inspect the facilities, and evaluate the program. Presumably the same consideration would apply to teaching animal science students. If animal science students were taught to perform laparotomies to collect embryos for embryo transplantation, the activity would be a teaching activity rather than an agricultural activity, and would therefore be regulated.

In a July 13, 1992 USDA policy memorandum (USDA, 1992b), USDA determined that if biologics were produced in farm animals for farm animals, the activity was agricultural and therefore not regulated. On the other hand, if the biologic was produced in farm animals for human beings or for nonfarm animals, then the activity was "biomedical" and the activity was regulated. In other words, if one horse produced tetanus antitoxin for use in horses, then agricultural standards would apply. On the other hand, if the horse in the next stall produced tetanus antitoxin for use in humans, then the activity would be "biomedical" and the activity would be regulated as biomedical research under the Animal Welfare Act.

THE RED RUBBER BALL

A newly appointed IACUC beginning a facility inspection with two or three different books of standards in their hands could easily feel a bit unnerved. All the more so since the standards for both biomedical and agricultural research are certain to change. Both the *NIH Guide* and the *Ag Guide* are in the early phases of revision, and the new USDA standards for farm animals will probably be drafted during the next year or two. However sincerely an institution attempts to follow all existing guidelines, compliance may prove to be a moving target.

IACUCs that find themselves responsible for both agricultural and biomedical studies will find opportunities as well as challenges. Members of such an IACUC will find themselves in conversation with agricultural and biomedical scientists at a time when both communities are engaged in introspection about animal care. The concept of animal well-being and its relationship to handling and to environmental enrichment has become not only a point of contention, but also a respected area of research. Our regulatory agencies and professional bodies need research that critically evaluates the animals' needs from the animals' perspective. Only such information will allow them to write coherent, unitary standards based on science rather than on anthropomorphism or tradition.

IACUCs should remain open-minded and should not hesitate to use the considerable professional judgement that the *NIH Guide*, the *Ag Guide*, and even the Animal Welfare Act regulations allow them. IACUCs that keep themselves informed about current issues in animal care will find that they can offer considerable assistance to the agricultural, biomedical, and regulatory communities during this period of change.

The appointment of an IACUC and creation of its charge is one of the most important administrative acts a Chief Executive Officer performs. Chief Executive Officers should appoint people they trust, people whose opinions they respect, people who believe in science, and people who represent a broad enough spectrum of the campus community to speak for the institution as a whole.

REFERENCES

American Association for the Accreditation of Laboratory Animal Care (AAALAC). 1991. AAALAC Accreditation Program.

Consortium for Developing a Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching. 1988. Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching. (Available at a cost of $5.00 each from Association Headquarters, 309 West Clark Street, Champaign, IL 61820. Tel: 1-217-356-3182.)

National Research Council (NRC). 1985. Guide for the Care and Use of Laboratory Animals. A report of the Institute of Laboratory Animal Resources Committee on Care and Use of Laboratory Animals. Washington, D.C.: U.S. Department of Health and Human Services.

National Science Foundation (NSF). 1985. Policy on the Use of Animals in Research. Section 713 in National Science Foundation Grant Policy Manual.

North, M. O. 1984. Commercial Poultry Production Manual. Westport, Conn.: AVI Publishing Company.

U.S. Department of Agriculture (USDA). 1990. Policy Memorandum, Deputy Administrator Arnoldi to REAC Personnel, August 28.

U.S. Department of Agriculture (USDA). 1992a. Policy Memorandum, Staff Veterinarian DePoyster to Sector Supervisors and Animal Care Specialists, April 23.

U.S. Department of Agriculture (USDA). 1992b. Policy Memorandum, Staff Veterinarian DePoyster to Animal Care Specialists, July 13.

U.S. Food and Drug Administration (FDA). 1992. Position Paper on Animal Use in Testing FDA-Regulated Products, October 7, 1992.

Commentary: Farm Animal Use in Biomedical Science—Melding the Guidelines[a]

Stanley E. Curtis

INTRODUCTION

Biomedical researchers and teachers are turning more and more to using farm animals as model subjects. As organizers of the 1993 meeting in Oklahoma City rightly observed, "The use of farm animals in research and education presents a special challenge to today's scientists, educators, and regulatory agencies."[a] Why? Consider the following two reasons:

- There are apparent differences between the standard husbandry practices for animals as outlined in the *Guide for the Care and Use of Laboratory Animals* (*NIH Guide*) (NRC,

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[a]This article is adapted from Dr. Curtis's keynote address at the workshop *Farm Animals: Present and Future Use in Research and Education* sponsored by the National Institutes of Health, Office for Protection from Research Risks of the U.S. Public Health Service and the University of Oklahoma Medical Center and the open forum *Farm Animals: Issues Under the Animal Welfare Act* sponsored by the Animal and Plant Health Inspection Service, Regulatory Enforcement and Animal Care of the U.S. Department of Agriculture at the University of Oklahoma Medical Center, Oklahoma City, 27-29 September 1993.

1985) and in the *Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching* (*Ag Guide*) (Consortium for Developing a Guide, 1988). These are discrepancies in important aspects of animal care—excrement accumulation, temperature control, pest management, ventilation rate, specifications for surfaces, and even in some cases frequency of observation. Can differences such as these be explained? What are their scientific bases?

- Animal activists are satisfied by neither set of guidelines and are especially critical when the two husbandry standards *seem* to be so disparate. They question how an animal's well-being can be protected by both sets of guidelines. Such criticism has left some biomedical scientists wondering, for example, whether federal policy and law permit them to use animals purchased from farmers who did not follow the biomedical standards of care when the creatures were in their charge.

The purpose of this article is to suggest (1) that the two sets of guidelines used by the scientific community for the care and use of farm animals (the *NIH Guide* and the *Ag Guide*) be melded or harmonized, and (2) that the federal government's policies and regulations come to reflect this approach. In this way, farm animals could be cared for in systems ranging from conventional laboratory animal facilities to well-designed, well-managed commercial farms regardless if the research were agricultural or biomedical in nature.

Moreover, the decision whether a facility or university system would be "exempt" from federal inspection—as described by the Animal Welfare Act and its amendments—could be based not on the outcome of the research (whether biomedical or agricultural in nature), but on the specific requirements of the protocol. If the research or education *must* be conducted in a farm setting to meet its objectives, the protocol would be exempt from inspection.

Two ideas should be kept in mind when considering the differences between the two sets of guidelines, which I hope ultimately will be found sensible and will be adopted. First, the very natures of these special animals we humans domesticated thousands of years ago has made them extremely adaptable to various situations, and, perhaps more importantly, as dependent on humans as humans are on them. Secondly, the different kinds of animal research and teaching that occurs in agricultural science and biomedical science impacts on how the animals need to be maintained.

THE NATURE OF FARM ANIMALS

Farm animals are fundamentally different than most traditional laboratory animals. One of the more obvious examples is that most farm animals are bigger than most laboratory animals. Geometry tells us that the surface-to-mass ratio of a 100 g rat is greater than that of a 100 kg ram, and much greater than that of a 1000 kg bull. Physics then tells us that the rat is more sensitive to hot and cold environments than is the ram and especially the bull. In other words, the thermoneutral zones of the ram and the bull, respectively, are wider than that of the rat. Of course, those livestock and poultry that are small—hatchlings and neonates, for example—are also very sensitive to their thermal surroundings, and farmers go to great lengths to protect these animals from both cold stress and heat stress.

All creatures respond to thermal stressors by moving to a more favorable place; that is, if one is available and accessible. A horse at pasture can use a run-in shed as a sunshade in summer and as a shield against freezing rain in winter. It thus thermoregulates behaviorally. A mouse in a hanging cage has limited mobility, thus limited ability to move to a more favorable place. The mouse needs more protection and more environmental safeguards than does the horse.

Genetics is an additional important consideration. In general, outbred livestock and hybrid poultry are constitutionally sturdier than inbred laboratory animals. In other words, consistent with common observations, mongrels are tougher than purebreds.

DOMESTICATION—A MUTUAL CHOICE

Perhaps the most important factor in the unique nature of farm animals is domestication. We humans have domesticated but a tiny fraction of all the animal species on earth. Why cattle but not antelope? Why dogs but not hyenas? Why chickens but not eagles?

Stephen Budiansky, in his book *The Covenant of the Wild: Why Animals Chose Domestication* (1992), talks about the extraordinarily high failure rate of the human as domesticator:

> Indians kept moose, raccoons, and bears as pets, but not one exists as a domesticated species today. The ancient Egyptians, whose very civilization was based on cattle herding and who were well-versed in the mysteries of animal husbandry, tried but failed to domesticate gazelles, ibex, hyenas, and antelope. . . . Yet even for this highly developed agricultural civilization, such experiments led to naught. By contrast several thousand years earlier, the very first agriculturists, people who had never built a fence or mowed a hayfield, succeeded in domesticating virtually every animal that even today, more than five thousand years later, occupies a place of importance in our homes and fields. (Budiansky, 1992, p. 23).

A few more instructive insights from Budiansky's book help describe the relationship of humans to domesticated animals:

> The urge to turn animals either into things or into people reflects the distance we have traveled in a generation or two. We conveniently alternate between anthropomorphism and blindness. (p. 3)

> The conception of nature that sees everything bad as man's doing and thus man's responsibility is a powerful force. (p. 6)

> Sweden passed a law in 1988 actually requiring cows, pigs, and animals raised for fur to be kept 'in as natural an environment as possible,' begging the question of what is natural for animals that are by their evolutionary heritage incapable of surviving in the wild. It is unnatural to feed a cow hay in the winter, for example; it is unnatural for cows even to *be* in Sweden in the winter in the twentieth century, for that matter. Wild cows became extinct in Europe thousands of years ago. Still, the law specifically requires that cows must be allowed to graze on pasture in the summer. In a bow to reality, it doesn't mind if cows are shut up in a warm barn in the winter. (pp. 11–12)

> If all of these moves [by well-meaning but naive animal-protection activists] are incomprehensible to hunters, farmers, and the few others in our modern world whose daily work still brings them into contact with animals, it is not because they [hunters, farmers, etc.] are without compassion. It is because they know better. . . . They know that domesticated animals need us as we need them. (p. 12)

> If life with man was a better evolutionary bargain for domesticated animals than was life in the wild, then it makes no sense to say that nature . . . ends where man's presence begins. And it raises doubts about larger judgments based on the premise that whatever is wild is pristine, whatever is human is tarnished. We are easily shocked by the horror stories of the laboratory and barn in part because we are ignorant of the greater horrors of the wood and water, horror stories written by nature herself. (p. 14)

Budiansky concludes, "The only way out is to recognize that, in an evolutionary sense, domesticated animals chose us as much as we chose them" (Budiansky, 1992, p. 24).

CHARACTERISTICS OF DOMESTICATED ANIMALS

What characteristics made farm animals more amenable to domestication than their cousins in the first place? E. B. Hale listed behavioral characteristics he termed either favorable or unfavorable to domestication (1969). These same traits would also seem a suitable list of favorable or unfavorable characteristics of animals used for research. Hale found the following traits favorable for domestication:

- large social groups
- social dominance orders
- males affiliated with a female group
- promiscuous mating
- males dominate females
- sexual signals involve movements or postures
- a critical period in development of the species bond
- females accept other young soon after parturition or hatching
- precocial young
- short flight distance to humans
- little disturbed by humans or sudden changes in the environment
- omnivorous
- adaptable to a wide range of environmental conditions
- limited agility

The following behavioral traits, characterized as unfavorable for domestication by Hale, cause difficulties for those who work in laboratory settings with species that never were domesticated:

- family groupings
- territorial social structure
- males in separate groups
- pair-bond matings
- male must either establish dominance over or appease female
- sexual signals provided by color markings or morphological structures
- species bond established on basis of species characteristics
- young accepted on basis of species characteristics
- altricial young
- extreme wariness and long flight distance to humans
- easily disturbed by humans or sudden changes in environment
- specialized dietary habits
- require a specific habitat
- extreme agility

TRANSLATING KNOWLEDGE INTO PRACTICE

While it seems simple to care for an animal, there are various ways to fulfill its needs and support its well-being. Whether a heifer resides in a laboratory animal facility on the third floor of a medical school in downtown Saint Louis or on the back section of a land-grant college's experimental ranch in the foothills of the Sierra Nevada, she has individual needs to support her well-being. This is the main point supporting the wisdom of goal-oriented performance specifications in animal care as opposed to process-oriented design or engineering specifications.

Additionally, those of us engaged in animal care are in the process of perfecting both our understanding of what constitutes well-being and our grasp of the practical means to support it. This process of discovery involves scientifically studying animals to learn more about their needs and how to meet them. We are fortunate because we already know much about the nature of farm animals, largely because they are crucial to the health and well-being of humans, and indeed to the practice of agriculture all over the world. Still, new perspectives come along, such as Budiansky's (above).

Is it any wonder that farm animals flourish both in biomedical laboratories and on farms and ranches? Is it really surprising that guidelines for the care of farm animals in the two settings—developed by people with experience working primarily in either one place or the other—would be different? Once we recognize the natural histories of these won-

derful animals, and once we appreciate the different needs of scientists working in the two arenas, is there any reason why the two sets of guidelines could not be melded?

With respect to farm animals, I submit that the two guides are *not inconsistent* with each other. They deal with special animals, and simply reflect different ranges on a wide continuum of acceptable care situations. The existing differences between the two guides are products of poor communication between the two communities of scientists—the agricultural and the biomedical—responsible for their development. The meeting in Okahoma City in 1993[a] was designed to facilitate better communication along this line and begin correcting this situation.

AGRICULTURAL VERSUS BIOMEDICAL RESEARCH AND TEACHING

The meeting organizers alluded to this when they said, "the unique needs of each species may vary according to the study objectives. . . ."[a]

Most biomedical research that uses animals is *basic*; the animal "model" is used to better understand a target species, usually humans. Variables must be strictly controlled in basic research in order to maintain the integrity of results. However, when humans serve as target-species subjects in *clinical* studies, significant covariables usually are less rigidly controlled than in basic biomedical experiments, because it is important to know that what is being tested (whether an experiment, drug, or therapy) will produce similar results in a wide variety of settings. Most agricultural research—in particular, those experiments requiring that the animals be kept in real or simulated agricultural settings—is akin to clinical research in biomedical science, in which the target species serves also as the experimental subject. Scientists using farm animals as target-species subjects in agricultural research need to study them under the variable conditions typical of farms and ranches. The reality of these environmental covariables is the reason both clinical medical researchers and applied agricultural investigators must conduct much of their work in real or simulated settings instead of under the more closely controlled, artificial conditions needed by basic scientists in both arenas.

The difference in how a nanny responds to experimental treatments in Gainesville, Florida compared with Ithaca, New York or Pullman, Washington is of interest to goatherders in Florida, New York, and Washington. The responses of this goat in a closely controlled environment, while of great interest to scientists, are less interesting to a goatherder. For this reason, there are agricultural experiment stations scattered all over the country. For the same reason the *Ag Guide* at one point reads:

> In many cases, the facilities in which these animals reside must simulate conditions on commercial farms; otherwise, the results may be biased. . . . The pertinent systems include range or pasture production in naturalistic settings, various degrees of confinement in certain less extensive production systems, and various degrees of confinement in more intensive production systems, including enclosed housing (Consortium for Developing a Guide, 1988, p. 2).

GRAY AREAS

A political artifact—namely, the food and fiber research exemption in the Animal Welfare Act and its amendments—has created many confusing and contradictory situations. We have let this legislative oddity, which makes no sense at all in terms of animal needs, drive regulatory activity that presumably was originally intended to safeguard the well-being of animals and nothing more.

Do farm animals in biomedical research need to be cared for according to protocols that have evolved for the sound care of laboratory animals in general? In most cases, for supporting animal well-being, I would say, no. Because they are highly adaptable and relatively unfinicky, farm animals will thrive in either setting. However, the particular protocol may require a more closely controlled situation. Apart from any scientific requirements, if an animal's well-being is completely supported in a setting typical of a well-designed, well-managed farm, is there any reason it should be kept under a husbandry system that is known to be careful to an unnecessary extent?

If animals are being used in an experiment that does not deal directly with food and fiber production and thus does not require that they reside in a production setting, should they be exempt from certain laboratory animal care policies and regulations? Consider a hypothetical vitamin known to be problematic in human nutrition but not in the nourishment of pigs. If the National Institutes of Health were funding an experiment in an animal science department in which this vitamin was to be investigated using pigs as models for humans, should the care of the pigs be exempt from certain Animal Welfare Act regulations?

CONCLUSION

If the *NIH Guide* and the *Ag Guide* were integrated and published as one, then agricultural scientists and biomedical scientists alike could keep their farm animals in care systems ranging from conventional laboratory animal facilities to well-designed, well-managed commercial farms, satisfied that the animals' well-being was being supported across this wide continuum. The choice of system then could be based on the user's personal preference, the institution's capabilities, or any requirements of the science being done. This approach, incidentally, is much like the one now taken by the National Institutes of Health, Office for Protection from Research Risks. Finally, the U.S. Department of Agriculture's decision whether the facility were "exempt" from federal inspection could be based on whether the research or education must be conducted in a farm setting to meet its objectives.

REFERENCES

Budiansky, S. 1992. The Covenant of the Wild: Why Animals Chose Domestication. New York: William Morrow.

Consortium for Developing a Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching. 1988. Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching. (Available at a cost of $5.00 each from Association Headquarters, 309 West Clark Street, Champaign, IL 61820. Tel: 1-217-356-3182.)

Hale, E. B. 1969. Domestication and the evolution of behaviour. Pp. 22-42 in The Behaviour of Domestic Animals, E. S. E. Hafez, ed. Baltimore, Md: Williams and Wilkins.

National Research Council (NRC). 1985. Guide for the Care and Use of Laboratory Animals. A report of the Institute of Laboratory Animal Resources Committee on Care and Use of Laboratory Animals. Washington, D.C.: U.S. Department of Health and Human Services. (Single copies available from Office for Protection from Research Risks, Division of Animal Welfare, National Institutes of Health, 6100 Executive Boulevard, MSC 7507, Rockville, MD 20892-7507. Tel: 1-301-496-7163.)

In the News

AAALAC Honored Nationally by AVMA and ACLAM

Dr. Albert E. New, Executive Director of the American Association for Accreditation of Laboratory Animal Care (AAALAC), and Dr. Kathryn A.L. Bayne, AAALAC's Associate Director for Accreditation were independently recognized for leadership and achievement during the annual American Veterinary Medical Association (AVMA) meeting in San Francisco, California.

Dr. New was selected by the AVMA to be the recipient of the Sixteenth Annual Charles River Prize. The prize, awarded by the Charles River Foundation, recognizes the distinguished contributions to the field of laboratory animal science by an AVMA member veterinarian. Dr. New, who received his D.V.M. from Kansas State University and an M.S. in Laboratory Animal Medicine from Texas A&M University, is lauded as a dedicated scientists and astute administrator and recognized as an accomplished researcher, educator, and spokesman. His research interests include defining and improving animal models for investigation, primatology, cancer, physiology, reproduction, and nutrition. For 13 years, Dr. New was an Air Force Veterinary Corps Officer, during which time he held positions as Director of Veterinary Services, Naval Aerospace Medical Institute, Pensacola, Florida; head of the Veterinary Medicine Department, Taipei, Taiwan; and Chief, Research Support Branch, Wright-Patterson Air Force Base in Ohio. He served as a U.S. Public Health Service Officer with the National Institutes of Health for 13 years. Dr. New has also held posts as Head of the Primate Quarantine, Assistant Chief of Veterinary Resources, and Director of Laboratory Animal Science for the National Cancer Institute. He has been the recipient of the "Gold Star Award—Outstanding Contributions to Veterinary Medicine" from the State of Florida.

Dr. Bayne is the recipient of the Henry and Lois Foster Award presented in conjunction with American College of Laboratory Animal Medicine (ACLAM) activities at the AVMA meeting. This award recognizes academic excellence in laboratory animal medicine in recognition of achieving the highest score on the 1993 board certifying practical examination. Dr. Bayne is a member of the Institute of Laboratory Animal Resources (ILAR) Committee to Revise the *Guide for the Care and Use of Laboratory Animals* and the Committee on Well-being of Nonhuman Primates. She earned her masters in experimental psychology, and doctorates in wildlife biology and veterinary medecine from Washington State University. Dr. Bayne is recognized for her contributions in animal behavior and environmental enrichment of various animal species.

Annual Harry C. Rowsell Award Presented to Franklin M. Loew

The Scientists Center for Animal Welfare (SCAW) presented the second annual Harry C. Rowsell Award to Franklin M. Loew, D.V.M., Ph.D., Dean, School of Veterinary Medicine, Tufts University, Boston. The award is given in honor of Dr. Rowsell who is known for his commitment in fostering the dual goals of good science and the humane treatment of laboratory animals.

An internationally known lecturer and writer on animals and society, Dr. Loew has been particularly involved in contentious issues such as the use of animals in research, the changing moral status of animals, and what he calls the "urban prism" through which most North Americans and Europeans now view domestic animals and wildlife. He has testified on these issues before the U.S. Congress on many occasions.

Dr. Loew is in his thirteenth year as Dean of the School of Veterinary Medicine at Tufts University, as well as its Foster Professor of Comparative Medicine and Chair of the School's Department of Environmental Studies. He is also President of Tufts Biotechnology Corporation. A former chairman of the Institute of Laboratory Animal Resources' Council, Dr. Loew holds two degrees from Cornell University and one from Canada's University of Saskatchewan, where he spent 10 years as Professor and Director of the Animal Resources Centre. He was then at the Johns Hopkins University School of Medicine for 5 years where he was Director of the Division of Comparative Medicine before coming to Tufts in early 1982.

National Survey of Laboratory Animal Use, Facilities, and Resources

In January 1995, the National Center for Research Resources (NCRR) of the National Institutes of Health (NIH) will be conducting a national survey to characterize the use of laboratory research animals. All institutions receiving Public Health Service (PHS) funding are requested to participate in this confidential survey to ensure the validity of the returned information.

Data gathered will be reported in aggregate formats and used to characterize the needs for laboratory animals in the research community, the current use of animals, and the impact of regulatory compliance. Your response to this survey will contribute to a database of information that will impact future federal allocations for laboratory animal resource funding, facility renovation programs, and projected goals of the NIH as they relate to biomedical research.

All institution's surveyed will receive a copy of the survey analysis report, which will provide statistical data on facility types, cost accounting procedures, animal species in use, and personnel resources involved in laboratory animal sciences in the United States.

Coming Meetings

January 1995

12–13 Considerations for Use of Wild Vertebrates in Research—Tucson, Arizona. This workshop, sponsored by the National Institutes of Health, Office for Protection from Research Risks, the Northern Arizona University, and the University of Arizona, will focus on three general themes related to the inclusion of native vertebrates in research: (1) federal institutional policies and procedures as they relate to the responsibilities of the institutional animal care and use committee (IACUC) in considering research on both captive and free-living wild vertebrates, (2) standards for the husbandry and housing of captive wild vertebrates, and (3) occupational health considerations with an emphasis on rodent-borne hantavirus. This workshop is part of an ongoing series sponsored by the National Institutes of Health, Office for Protection from Research Risks on implementing the *Public Health Service Policy on Humane Care and Use of Laboratory Animals*. Workshops are open to institutional administrators, members of IACUCs, laboratory animal veterinarians, investigators, and other institutional staff who have responsibility for high-quality management of sound institutional animal care and use programs. Ample opportunities will be provided to exchange ideas and interests through question and answer sessions and informal discussions. For more information contact Dr. Susan Sanders, Director, University of Arizona Animal Care, 2205 E. Speedway Boulevard, Tucson, AZ 85719. Tel: 1-602-621-3454; Fax: 1-602-621-3355.

March 1995

13–14 Animal Care and Research: Challenges and Changes for the Institutional Animal Care and Use Committee—San Diego, CA. Sponsored by the National Institutes of Health, Office for Protection from Research Risks, Tufts University School of Veterinary Medicine, and Public Responsibility in Medicine and Research (PRIM&R), this workshop will focus on revisions to the *Institutional Animal Care and Use Committee Guidebook*, assessment and reduction of pain and distress in animal research, occupational health risks and biohazards, and a host of other regulatory and administrative issues that are central to the successful operation of laboratory animal care and research programs. This workshop is part of an ongoing series sponsored by the National Institutes of Health, Office for Protection from Research Risks on implementing the *Public Health Service Policy on Humane Care and Use of Laboratory Animals*. Workshops are open to institutional administrators, members of institutional animal care and use committees, laboratory animal veterinarians, investigators, and other institutional staff who have responsibility for high-quality management of sound institutional animal care and use programs. Ample opportunities will be provided to exchange ideas and interests through question and answer sessions and informal discussions. Immediately preceding the conference, Applied Research Ethics National Association (ARENA) will sponsor its annual animal issues meeting on Sunday, March 12. For more information contact Ms. Danielle Demko, PRIM&R, 132 Boylston Street, Boston, MA 02116. Tel: 1-617-423-4112; Fax: 1-617-423-1185.

April 1995

19–21 Animals in Science: Perspectives on their Use, Care, and Welfare—Clayton, Victoria, Australia. This conference, sponsored by the Research Ethics Unit of Monash University and the Australian Humane Research Foundation, will present perspectives on the care, use, and welfare of laboratory animals. Adjuncts and alternatives to animal use will be discussed, both in research and teaching. Different points of view will be given on a number of topics. For more information contact Dr. Noel E. Johnston, Research Ethics Unit, Monash University, Clayton, Victoria 3168, Australia. Tel: 61-3-905-3037; Fax: 61-3-905-3866; Email: noel.johnston@adm.monash.edu.au.

May 1995

8–9 The Well-being of Animal Research Models in Zoos and Aquaria—New Orleans, Louisiana. This 2-day international conference will focus on areas of concern regarding animals used for research in U.S. zoos and aquaria. The conference is sponsored by the Scientists Center for Animal Welfare (SCAW) and the American Veterinary Medical Association. General sessions include discussions on how research concerns differ in zoos and aquaria, ethical dilemmas for conservation research, trends in environmental enrichment, and the role of the institutional animal care and use committee at zoos and aquaria. For more information contact SCAW, Golden Triangle Building One, 7833 Walker Drive, Suite 340, Greenbelt, MD 20770. Tel: 1-301-345-3500; Fax: 1-301-345-3503.

June 1995

11–14 CALAS/ACTAL Annual Conference—Saskatoon, Saskatchewan, Canada. The Thirty-Fourth Annual Conference of the Canadian Association for Laboratory Animal Science/L'association canadienne pour la technologie des animaux de laboratoire (CALAS/ACTAL) will include workshops and scientific sessions in laboratory animal science. For more information contact Dr. Don McKay, CALAS/ACTAL National Office, Biosciences Animal Service, CW 401 Biological Sciences Building, Edmonton, Alberta, Canada T6G 2E9. Tel: 403-492-5193; Fax: 403-492-7257; Email: dmckay@gpu.srv.ualberta.ca.

24–29 Ethical Issues of Animal Research—Washington, D.C. This summer course is open to college faculty and others who would like to improve their skills in teaching about ethical issues surrounding the use of animals as research subjects. Emphasis will be on how to use the course material in classroom instruction. Topics include the moral status of nonhuman animals, justification for using animals as experimental subjects, ethical concerns about vulnerable subjects, student objections, the use of alternatives, animal harms and pain, legal issues, and the importance of species. For more information contact Moheba Hanif, Georgetown University, Washington, D.C. 20057. Tel: 1-202-687-6833; Fax: 1-202-687-8089; Email: hanifm@guvax.georgetown.edu.

September 1995

14–15 Internal Audits of the Animal Care and Use Program—Augusta, Georgia. Sponsored by the National Institutes of Health, Office for Protection from Research Risks, the Medical College of Georgia, and Albany State College, this workshop will address processes by which institutional animal care and use committees (IACUCs) can effectively evaluate their institutions' animal care and use program. The *Public Health Service Policy on Humane Care and Use of Research Animals* (*PHS Policy*) and U.S. Department of Agriculture (USDA) regulations state that at least once every 6 months the institution's program is to be evaluated by the IACUC using the *Guide for the Care and Use of Laboratory Animals* (*Guide*) and USDA regulations (Title 9, Chapter 1, subchapter A-Animal Welfare) as a basis. Topics include a review of the program as described in the *Guide*; institutional policy issues such as the occupational health and safety program, personnel training, and the activities of the IACUC and how effectively it meets its mandates; veterinary care; the animal environment; and record reviews. Reports of the IACUC semiannual program and facility reviews will also be discussed. Approaches useful to IACUCs serving both small and large institutions will be included. This workshop is part of an ongoing series sponsored by the National Institutes of Health, Office for Protection from Research Risks on implementing the *PHS Policy*. Workshops are open to institutional administrators, members of IACUCs, laboratory animal veterinarians, investigators, and other institutional staff who have responsibility for high-quality management of sound institutional animal care and use programs. Ample opportunities will be provided to exchange ideas and interests through question and answer sessions and informal discussions. For more information contact Ms. Katrinka Akeson, Department of Continuing Education HM 100, Medical College of Georgia, Augusta, GA 30912. Tel: 1-706-721-3967; Fax: 1-706-721-4642.

January 1996

27–31 Fourth National Symposium on Biosafety: Working Safely with Research Animals—Atlanta, Georgia. This national symposium is sponsored by the Centers for Disease Control and Prevention, Office of Health and Safety; National Institutes of Health, Office for Protection from Research Risks; American Biological Safety Association; and Emory University School of Medicine and Yerkes Primate Center. It is intended to provide a forum to stimulate an exchange of ideas and information that promote the identification of hazards, assessment of risks, and implementation of measures to ensure the health and safety of personnel and animals. Biosafety officers, occupational health physicians, veterinarians, principal investigators, members of institutional animal care and use committees, architects, engineers, animal care givers and supervisors, facility managers, administrators, and others are encouraged to attend. For more information contact Centers for Disease Control and Prevention, Office of Health and Safety, Atlanta, GA 30333 (Attention: Jonathan C. Richmond, Ph.D.). Fax: 1-404-639-2294.

June 1996

19–26 Sixth FELASA Symposium on International Harmonization of Laboratory Animal Husbandry Requirements—Basel, Switzerland. The aim of this symposium is

to exchange useful information among scientists and regulatory agencies in order to increase our knowledge and harmonize the requirements of laboratory animal husbandry. For more information, contact Sixth FELASA Symposium, Kongresszentrum Messe Basel, Messeplatz 21, CH-4021 Basel, Switzerland. Tel: 61-686-2828; Fax: 61-686-2185.

October 1996

20–25 Second World Congress on Alternatives and Animal Use in the Life Sciences—Utrecht, The Netherlands. The aim of this congress is to exchange information on recent developments in the field of alternatives (replacement, reduction, refinement) within the various areas of animal use, such as toxicology, pharmacology, pharmacy, cancer research, bioassays, and safety testing. Alternatives in education and training, ethical aspects of animal use and developments aiming at the improvement of animal welfare will be covered. For more information contact World Congress Alternatives 1996, FBU Congress Agency, P.O. Box 80.125, 3508 TC Utrecht, The Netherlands. Tel: 31-30535044; Fax: 31-30533667.

New Books

Summary: Manual of Microbiologic Monitoring of Laboratory Animals, Second Edition

Forty-eight international experts in microbiology contributed manuscripts for this manual that was developed under a U.S./Japanese Research and Development Cooperative Program. The result of these efforts is a greatly expanded document compared with the first edition, published in 1986.

"The purpose of this manual is to provide information on the microbiologic monitoring of rat and mouse colonies. It is especially oriented toward providing useful information to decision-makers responsible for colony management," the editors write in the introduction. The material presented in this manual fulfills this objective extremely well. The introduction contains an in-depth perspective and guidance on monitoring rat and mouse colonies with a list of infectious agents considered to be pathogens or agents that potentially compromise the quality of research data.

The text of the manual consists of presentations on selected agents likely to be monitored routinely or under special circumstances. The 43 agents included in the manual are divided into three sections: (1) viruses; (2) bacteria, mycoplasma, and fungi; and (3) parasites. Generally, the presentation on each agent is divided into four parts.

Part one provides information on the agent's morphology and cultivation, the known strains, and its stability or inactivation. Part two, "Characteristics of Infection," provides information on issues related to the geographic distribution of the agent, the means of spread, morbidity and mortality, prevalence, pathology, diagnosis, and interference with research. Part three of each agent presentation is on control and prevention, and information is provided on special considerations, the effectiveness of vaccines, and the effectiveness of hysterectomy derivation. The last section discusses isolation of the agent and provides information on testing procedures such as serology, histology, or histopathology.

This manual is written in a clear and concise manner and is an excellent reference document; complete and up-to-date references are included with each agent. It will be a welcome addition to the personal libraries of microbiologists, laboratory animal veterinarians, animal facility managers, and students of laboratory animal science.

Scientists involved with laboratory animals in developing nations throughout the world, where literature related to laboratory animals is not readily available, will greatly benefit from the manual because of the useful information provided.

Joseph J. Knapka, Ph.D.
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Veterinary Resources Program
National Center for Research Resources
National Institutes of Health

Manual of Microbiologic Monitoring of Laboratory Animals, Second Edition, Kim Waggie, Naoko Kagiyama, Anton M. Allen, and Tatsuji Nomura, eds., National Institutes of Health, National Center for Research Resources, 226 pp., bound paperback, $21.00, NIH Publication No. 94-2498. (Available from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402. Tel: 1-202-783-3238. Refer to stock no. 017-040-00531-8). Interested parties from developing nations may be eligible for a free copy. For more information write Chief, Laboratory Animal Sciences, Laboratory Sciences Section, Veterinary Resources Program, National Center for Research Resources, National Institutes of Health, Building 28A, Room 111, Bethesda, MD 20892.

The Role of the Chimpanzee in Research, G. Eder, E. Kaiser, and F.A. King, eds. Presented by leading scientists to mark the opening of the Hans Popper Primate Center, the contributions in this volume cover a broad spectrum of topics relating to the use of the chimpanzee in research. The first section of the book discusses the history of primate research and relates it to human experimentation. Political

and ethical aspects of animal research are also thoroughly explored. The second section contains papers on chimpanzee and human development, behavior, and reproduction, and provides detailed information on the breeding and care of chimpanzees in captive populations in the U.S. The third and most extensive section of the book deals with the role of the chimpanzee in biomedical research. Emphasis is placed on research into infectious diseases, particularly hepatitis, as well as on the testing of vaccines and safety testing of blood products. Karger, 1994, 204 pp., hard cover, $182.50, ISBN 3-8055-5850-3. (For more information contact S. Karger AG, PO Box CH-4009 Basel, Switzerland; or, S. Karger Publishers, Inc., 26 West Avon Road, P.O. Box 529, Farmington, CT 06085.)

Principles of Laboratory Animal Science: A Contribution to the Humane Use and Care of Animals and to the Quality of Experimental Results, L.F.M. van Zutphen, V. Baumans, and A.C. Beynen, eds. This book contains basic facts and principles covering the main theoretical aspects of this subject, encompassing welfare as well as ethical issues. After a general introduction and a glimpse into legislation, information is presented on the biology and husbandry of the most frequently used animal species and the relationship among behavior, stress, and well-being. The book also covers aspects of standardization, diseases of laboratory animals and their effect on welfare and experiment results, recognition of pain and distress, anesthesia, the possibilities and limitations of the use of alternatives, and the ethics of animal experimentation. Elsevier Science Publishers, 1993, 134 pp.; Hardbound, $185.75, ISBN 0-444-81487-6; Paperback, $77.25, ISBN 0-444-81487-6. (For more information contact Elsevier Science Publishers, P.O. Box 211, 1000 AE Amsterdam, The Netherlands; or, Elsevier Science Publishing Co., Inc., P.O. Box 945, Madison Square Station, New York, NY 10160-0757.)

Publications Available

Single copies of the following publications are available without charge from the Institute of Laboratory Animal Resources (ILAR), National Research Council, 2101 Constitution Avenue, NW, Washington, DC 20418. Tel: 1-202-334-2590; Fax: 1-202-334-1687.

Annotated Bibliography on Uncommonly Used Laboratory Animals: Mammals. 1986

Control of Diets in Laboratory Animal Experimentation. 1978

*__Definition, Nomenclature and Conservation of Rat Strains.__ 1993

Guide to Infectious Diseases of Guinea Pigs, Gerbils, Hamsters, and Rabbits. 1974

Important Laboratory Animal Resources: Selection Criteria and Funding Mechanisms for their Preservation. 1990

Laboratory Animal Management: Cats. 1978

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Appendix 3

North American Free Trade Agreement

Impact on Biological and Agricultural Research and Trade

Discussion Paper prepared by the Institute of Laboratory Animal Resources

January 24, 1995

In the past year, the United States ratified the North American Free Trade Agreement (NAFTA) and the Uruguay Round of the General Agreement of Tariffs and Trade (GATT). Both agreements are aimed at reducing and eliminating barriers to trade, investment and services. Clearly both of these agreements signal the emergence of a "One World" Global Community and Market. At this time, it is impossible to identify all of the problems that will arise for Canada, Mexico, and United States in implementing them. Therefore, it is a certainty that there will be numerous challenges and opportunities for the various sectors within these countries.

With respect to agriculture, the negotiators established a set of principles to prevent the use of sanitary and phytosanitary standards as disguised barriers to trade. Both agreements make explicit a country's right to adopt and maintain any measures it believes necessary to protect the health of its animals and plants as long as the measures are based on science and are transparent. Wherever possible, these measures should be based on international standards.[1]

Other key provisions are: (1) Risk Assessment, (2) Equivalence, (3) Regionalization, (4) Role of International Standards Organizations, (5) Transparency, (6) Sanitary & Phytosanitary Committees, and (7) Consultations & Dispute Settlement.

Risk Assessment: The requirement that measures be based on science means that import decisions must be based on a risk assessment which uses scientific data and methodologies. Relevant factors include: the use of risk assessment methodologies and techniques developed by the international standards organizations; relevant inspection, sampling and testing methods; and disease/pest prevalence, etc.

Consultation & Dispute Settlement: The challenge as perceived by the negotiators, was how to create an acceptable approach to resolve trade disputes involving differences in regulatory standards. The solution is to encourage harmonization through the widest possible use of international standards and the creation of a dispute settlement system. Central to the dispute settlement system is the use of expert panels or boards, which will review disputes and provide findings and recommendations. Basic questions when reviewing an issue or complaint are: What is the relevant international standard or guideline? What is the expert advice of the relevant international standard setting body? What available scientific data exists to support the measure subject to dispute?

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[1] In the NAFTA, Article 724 is **Definitions:** For the purposed of this Section: **international standard, guideline or recommendation** means a standard, guideline or recommendation: (b) regarding animal health and zoonoses, developed under the auspices of the International Office of Epizootics.

Laboratory Animal Management

DOGS

NATIONAL RESEARCH COUNCIL

Laboratory Animal Management

DOGS

Committee on Dogs
Institute of Laboratory Animal Resources
Commission on Life Sciences
National Research Council

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, National Academy of Engineering, and Institute of Medicine. The members of the committee responsible for the report were chosen for their special competencies and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, National Academy of Engineering, and Institute of Medicine.

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Any opinions, findings, and conclusions or recommendations expressed in this publication are those of the committee and do not necessarily reflect the views of DHHS, USDA, or other sponsors, nor does the mention of trade names, commercial products, or organizations imply endorsement by the U.S. government or other sponsor.

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Preface

It has been 2 decades since the Institute of Laboratory Animal Resources first published *Dogs: Standards and Guidelines for the Breeding, Care, and Management of Laboratory Animals* (National Academy of Sciences, Washington, D.C., 1973). During that period, great strides have been made in improving care and management techniques, making available specific-pathogen-free and purpose-bred dogs, and identifying dogs with precisely defined genetic disorders. The dog has proved to be "man's best friend," not only because it is considered a companion and family member, but also because its use in research has been associated with many breakthrough discoveries in human medicine (e.g., the discovery of insulin as a treatment for type I diabetes mellitus).

The same period has been characterized by increased public awareness and scrutiny of research funding, occupational health and safety, and animal welfare. New federal and state laws specifically intended to protect research animals have been promulgated and regulations established. In addition to presenting information relevant to the care and use of dogs in research and making recommendations based on an objective evaluation of that information, it was the committee's intent to incorporate in this report those aspects of canine husbandry embodied in federal law. Federal regulations and policies protecting dogs in research are therefore summarized in Chapter 1, which provides information for obtaining copies. Specific details of the regulations and policies are given throughout the text.

The committee firmly believes that good research requires a good animal-care program. The committee is also aware of the tremendous variation in physiologic traits among canine models. Dogs vary greatly in size, age, health status, physical conformation of the breed, behavioral characteristics, and experience. Therefore, no standard of animal care is likely to be optimal for all dogs. The committee recommends that performance standards be used with sound professional judgment in implementing the animal-care program.

Readers who detect errors of omission or commission or who have evidence to support improved procedures are invited to send suggestions to ILAR, National Research Council, 2101 Constitution Avenue, Washington, DC 20418.

The committee wishes to thank the entire staff of ILAR, but especially Dr. Dorothy Greenhouse and Ms. Amanda Hull, for assisting in the production of this manuscript. The committee also acknowledges the many fine contributions made to this report by scientists specializing in the care and use of dogs in research; their names appear on pages *iv* and *v*.

Fred W. Quimby, *Chairman*
Committee on Dogs

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1

Introduction

Dogs make valuable contributions in biomedical research because they share many biochemical and physiologic characteristics with humans and spontaneously develop disorders that are homologous to pathologic conditions in humans. While using them as models for human disease, we have also learned much about normal physiologic processes in dogs themselves. Advances in molecular genetics, reproduction, behavior, immunology, hematology, endocrinology, microbiology, nutrition, pharmacology, and oncology, to name a few, have made dogs more valuable as models and, at the same time, have provided veterinarians with useful information for the diagnosis and treatment of canine diseases.

In the past 2 decades, two amendments to the Animal Welfare Act (in 1976 and 1985) and a section added to the Health Research Extension Act of 1985 have resulted in revised standards for dogs. Institutions that use dogs must comply with the Code of Federal Regulations, Title 9, Subchapter A, Parts 1-3 (9 CFR 1-3), commonly called the Animal Welfare Regulations (AWRs), which were promulgated to administer the Animal Welfare Act. Institutions receiving Public Health Service (PHS) funding must also comply with the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* (hereafter called the *PHS Policy*) (PHS, 1986), which in turn requires compliance with the *Guide for the Care and Use of Laboratory Animals* (hereafter called the *Guide*) (NRC, 1985). Some of the AWRs are based on engineering standards (e.g., that on space requirements for dogs), but most rely on performance standards (i.e., the demonstration of

animal well-being). It is expected, therefore, that professional judgment will be used in applying the AWRs. It is also incumbent on all people using dogs to seek improvements in the methods for using them.

This edition of *Dogs: Laboratory Animal Management* incorporates features of housing, management, and care that are related to the expanded use of dogs as models of human diseases and an intrepretative summary of the AWRs and requirements of the *PHS Policy*. The appendix lists subjects within this text by page number with cross references to corresponding sections in the AWRs and the *Guide*. The regulations, policies, and guidelines that are applicable to dogs include the following:

- Code of Federal Regulations, Title 9, Subchapter A, Parts 1-3 (commonly called the Animal Welfare Regulations). Available from Regulatory Enforcement and Animal Care, APHIS, USDA, Federal Building, Room 565, 6505 Belcrest Road, Hyattsville, MD 20782 (telephone, 301-436-7833).
- *Public Health Service Policy on Humane Care and Use of Laboratory Animals*. Available in English or Spanish from the Office for Protection from Research Risks, Building 31, Room 5B59, NIH, Bethesda, MD 20892 (telephone, 301-496-7163).
- *Guide for the Care and Use of Laboratory Animals*. Available in English or Spanish from the Office for Protection from Research Risks, Building 31, Room 5B59, NIH, Bethesda, MD 20892 (telephone: 301-496-7163). Single copies (English only) available from the Institute of Laboratory Animal Resources, National Research Council, 2101 Constitution Avenue NW, Washington, DC 20418 (telephone, 202-334-2590).
- Code of Federal Regulations, Title 21, Part 58; Title 40, Part 160; and Title 40, Part 792 (commonly called the Good Laboratory Practice, or GLP, Standards). Available from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402 (telephone, 202-783-3238).
- IATA Live Animal Regulations. Available in English, French, or Spanish from the International Air Transport Association (IATA), 2000 Peel Street, Montreal, Quebec, Canada H3A 2R4 (telephone, 514-844-6311).

All animals used in research must be treated with the dignity and respect due living beings. Those who use animals in experiments must therefore be properly trained in methods appropriate for the species used. It is the responsibility of each research facility to develop educational programs for animal-care providers and the research staff (9 CFR 2.32). Recommendations for establishing such programs have recently been published (NRC, 1991).

REFERENCES

NRC (National Research Council), Institute of Laboratory Animal Resources, Committee on Care and Use of Laboratory Animals. 1985. Guide for the Care and Use of Laboratory Animals. NIH Pub. No. 86-23. Washington, D.C.: U.S. Department of Health and Human Services. 83 pp.

NRC (National Research Council), Institute of Laboratory Animal Resources, Committee on Educational Programs in Laboratory Animal Science. 1991. Education and Training in the Care and Use of Laboratory Animals: A Guide for Developing Institutional Programs. Washington, D.C.: National Academy Press. 139 pp.

PHS (Public Health Service). 1986. Public Health Service Policy on Humane Care and Use of Laboratory Animals. Washington, D.C.: U.S. Department of Health and Human Services. 28 pp.

2

Criteria for Selecting Experimental Animals

Scientists who are planning experiments evaluate both animal and nonanimal approaches. If there are no suitable alternatives to the use of live animals, the appropriate species is selected on the basis of various scientific and practical factors, including the following:

- Which species will yield the most scientifically accurate and interpretable results?
- According to critical review of the scientific literature, which species have provided the best, most applicable historical data?
- On which species will data from the proposed experiments be most relevant and useful to present and future investigators?
- Which species have special biologic or behavioral characteristics that make them most suitable for the planned studies?
- Which species have features that render them inappropriate for the planned studies?
- Which species present the fewest or least severe biologic hazards to the research team?
- Which species require the fewest number of animals?
- Which species that meet the above criteria are most economical to acquire and house?

For many scientific experiments, the answer to those questions will be the domestic dog, *Canis familiaris*. The size, biologic features, and coop-

erative, docile nature of the well-socialized dog make it the model of choice for a variety of scientific inquiries. The contributions of the dog to human health and well-being are numerous (Gay, 1984).

Although research with dogs is often primarily to benefit humans, it has also greatly benefited dogs that are kept as companion animals. Examples of the benefits to dogs are improvements in diagnostic techniques; treatments for diabetes and arthritis; surgical procedures for correcting or treating cardiovascular, orthopedic, and neurologic disorders; and therapies for bacterial, neoplastic, and autoimmune diseases. Moreover, dogs have been necessary for the development of vaccines that protect companion animals against viral diseases (e.g., distemper and parvovirus disease) and drugs that prevent parasitic diseases (e.g., dirofilariasis, or heartworm disease).

GENETIC FACTORS

All domestic dogs, irrespective of breed, are *Canis familiaris*. Canine genotypes and phenotypes vary among breeds as a result of selective breeding, which has created variations in allele frequency between breeds. Although "pure" breeds might have a higher frequency of some genes, much genetic variation remains in most breeds.

The canine karyotype consists of 78 chromosomes (Minouchi, 1928). Most of the autosomes are acrocentric or telocentric, and many pairs do not differ markedly in size. Recently, an improved method for staining canine chromosomes has been developed that makes karyotyping with Giemsa banding feasible (Stone et al., 1991).

A number of loci have been identified that code for the antigens of the canine major histocompatibility complex, which has been designated DLA (Vriesendorp et al., 1977). Initially, several alleles were defined with serologic techniques at three class I loci, and several alleles were defined with cellular techniques at a DLA class II locus (Bull et al., 1987; Deeg et al., 1986). Molecular techniques are being used to refine the definition of the DLA class I loci, and at least eight class I genes have been demonstrated in the dog (Sarmiento and Storb, 1989). Molecular-genetic studies to characterize canine class II loci correlate well with earlier work in which techniques for cell typing for class II antigens were used (Sarmiento and Storb, 1988a,b). The characterization of canine DLA loci is extremely useful for transplantation studies (Ladiges et al., 1985) and for demonstrating an association between the major histocompatibility complex and some inherited canine diseases (Teichner et al., 1990).

Attempts are under way to develop maps that identify the location of canine genes that control particular traits (e.g., inherited diseases and such behavioral tendencies as herding and aggression). Two approaches are used. The first relies on the principle that the relative positions of genes in a

particular region of DNA are comparable in humans, dogs, and other species. Conserved regions can be identified in DNA samples with restriction-fragment length polymorphisms (usually called RFLPs) that have been identified with probes for human and murine genes whose chromosomal locations are known. To enhance the detection of polymorphisms, investigators sometimes produce dog-coyote hybrids, cross-breed two widely divergent dog breeds, or analyze a large, well-defined canine kindred (Joe Templeton, Department of Veterinary Pathobiology, College of Veterinary Medicine, Texas A&M University, College Station, Tex., personal communication, 1993). The second approach uses simple sequence-repeat polymorphisms (microsatellite probes). Specific simple sequence-repeat markers that are highly polymorphic in dogs have been developed to study the canine genome (Ostrander et al., 1992, 1993). These and other techniques, such as chromosomal in situ hybridization and somatic cell hybridization, will likely greatly increase our understanding of canine genetics.

Inherited defects—including lysosomal storage diseases, retinal degenerations, coagulopathies, complement deficiency, and various musculoskeletal, hematopoietic, immunologic, and neurologic diseases—are common in purebred dogs, and many specific disorders are found most commonly in particular breeds (Patterson et al., 1989). This phenomenon might be related, in part, to breeders' inadvertent selection for mutant alleles that are closely linked to loci that determine breed-typical traits or to the chance increase in frequency of particular mutant alleles caused by the founder effect or random genetic drift. The high frequency of inherited canine disorders (compared with murine disorders) was recognized as early as 1969 (Cornelius, 1969). During the 20-year period 1960-1980, 20 percent of more than 1,200 literature citations on naturally occurring animal models of human diseases involved dogs (Hegreberg and Leathers, 1980). A compilation in 1989 noted that 281 inherited disease entities had been reported in dogs (Patterson et al., 1989). Many of those constitute the only animal models for investigating the corresponding human diseases (Patterson et al., 1988). The 19-fascicle *Handbook: Animal Models of Human Disease* (RCP, 1972-1993) lists 83 canine models of human diseases, many of which are hereditary, and the two-volume *Spontaneous Animal Models of Human Disease* (Andrews et al., 1979) describes many canine models.

In scientific studies in which genetic uniformity is desirable or in long-term studies in which the expected differences between experimental and control subjects are likely to be small, purpose-bred dogs (e.g., beagles) might be a more appropriate choice than dogs of unknown provenance. An advantage of using beagles, as opposed to other purpose-bred dogs, is the potential availability of other members of the kindred. But if the studies are to determine the greatest range of a variable that is likely to occur among the experimental subjects or if the experiments are of short duration, ran-

dom-source dogs might be more useful and less expensive (see "Procurement" in Chapter 5).

BIOLOGIC FACTORS

Dogs are monogastric carnivores with a short generation time (i.e., the calculated interval between when a pup is born and when its first offspring could be born) and a maximum life span of approximately 20 years; larger breeds appear to have a shorter maximum life span than smaller breeds. The canine mortality rate doubles every 3 years, compared with every 0.3 year for the rat (maximum life span, 5.5 years), every 15 years for the rhesus monkey (maximum life span, more than 35 years), and every 8 years for humans (maximum life span, more than 110 years) (Finch et al., 1990). Dogs are useful models for studying the lifetime effects of environmental factors, and there is an extensive literature on their use in radiation biology (see Gay, 1984; Shifrine and Wilson, 1980).

Selective breeding has resulted in a spectrum of behaviors and a large range of canine body sizes, from the giant breeds (e.g., Irish wolfhound), which can measure 91 cm (36 in) at the shoulder and weigh more than 56 kg (124 lb), to the toy breeds (e.g., Pomeranian), which can measure less than 31 cm (12 in) in height and weigh less than 4.5 kg (10 lb). Larger dogs, which can include mongrels or dogs of unknown breeding, are particularly well suited to cardiovascular, transplantation, and orthopedic studies, because body weights and blood volumes approximate those of humans (see Gay, 1984; Shifrine and Wilson, 1980; Swindle and Adams, 1988). The dog's size also lends itself to procedures that cannot be carried out in smaller species, e.g., when the instrumentation essential for collecting scientific data is bulky and cannot be miniaturized and when the resolution of imaging equipment requires a larger target field than is available in a small animal.

An individual dog often can be studied in great detail or in many ways, which might reduce the number of subjects needed for a study and generate a more definitive data set. For example, it is possible to take multiple blood samples of several milliliters each from a single dog over some period without compromising the dog's well-being, but taking samples of similar size during the same period from a single mouse or rat would be impossible.

BEHAVIORAL FACTORS

The social unit for dogs is the pack, and most dogs can be socialized to accept humans as the dominant individual in their social hierarchy, especially if the techniques used to socialize them provide rewarding experiences (e.g., food treats, petting, and verbal reinforcements) and minimize

TABLE 2.1 Selected Canine[a] Zoonoses

Disease in Humans	Agent	Mode of Transmission (Intermediate Host or Vector)[b]
Acariasis	*Cheyletiella yasguri*	Direct
Amebiasis	*Entamoeba histolytica*	Direct
American trypanosomiasis (Chagas' disease)	*Trypanosoma cruzi*	Indirect (triatomine insect)
Brucellosis	*Brucella canis*	Direct
Campylobacteriosis	*Campylobacter jejuni*	Direct
Coenurosis	*Taenia multiceps*	Direct
Colibacillosis	Enteropathogenic *Escherichia coli*	Direct
Cutaneous larva migrans	*Ancylostoma braziliense*	
	Ancylostoma caninum	Direct
Dipylidiasis	*Dipylidium caninum*	Indirect (dog flea)
Df2 infections	Dysgonic fermenter-2	Direct
Dirofilariasis	*Dirofilaria immitis*	
	Dirofilaria repens	Indirect (mosquito)
Giardiasis	*Giardia intestinalis* (*canis*)	Direct
Hydatidosis	*Echinococcus granulosus*	Direct
Larva currens	*Strongyloides stercoralis*	Direct
Leishmaniasis (cutaneous)	*Leishmania braziliensis peruviana*	Indirect (phlebotomine flies)
Leishmaniasis (visceral)	*Leishmania donovani*	Indirect (phlebotomine flies)
Leptospirosis	*Leptospira* spp. (usually *L. canicola*)	Direct
Pasteurellosis	*Pasteurella multocida*	Direct
Rabies	Rabies virus	Direct
Ringworm (dermatomycoses)	*Microsporum canis*	Direct
	Trichophyton mentagrophytes	
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Indirect (tick)
Salmonellosis	*Salmonella* spp.	Direct
Scabies	*Sarcoptes scabiei*	Direct
Tularemia	*Francisella tularensis*	Indirect (tick)
Visceral larva migrans	*Toxacara canis*	Direct
	Toxascaris leonina	
Yersiniosis	*Yersinia enterocolitica*	Direct

[a]North, Central, and South American dogs.

[b]Direct = transmission by direct contact with the dog, its excretions, or its secretions; no other vector or intermediate host is required.

aversive experiences. Different breeds and individual dogs differ in the ease and rapidity with which they can be socialized to humans (Scott and Fuller, 1965). However, properly socialized dogs can be docile and can be trained to cooperate in procedures that require repeated contacts with research personnel. For example, most dogs will allow venipuncture with

minimal restraint and will cooperate during detailed physical and neurologic evaluations.

HAZARDS

Unvaccinated dogs might harbor rabies virus, and preexposure immunization should be made available to personnel who are at substantial risk of infection (NRC, 1985). Dogs also have internal and external parasites that can be shared with humans (see "Parasitic Diseases" in Chapter 5). Table 2.1 lists selected zoonoses, zoonotic agents, and modes of transmission. Detailed discussions of zoonoses have been published (Acha and Szyfres, 1987; August, 1988; Elliot et al., 1985; Fishbein and Robinson, 1993; Hubbert et al., 1975). Personnel can develop allergies to canine dander and saliva, can be bitten or scratched, might suffer hearing impairment from prolonged exposure to excessive noise generated by barking dogs or mechanical equipment, or can be injured while lifting or transporting large dogs. To deal with these and other animal-related health problems, institutions must provide occupational health programs for personnel who work in animal facilities or have substantial animal contact (NRC, 1985).

REFERENCES

Acha, P. N., and B. Szyfres. 1987. Zoonoses and Communicable Diseases Common to Man and Animals, 2d ed. Scientific Pub. No. 503. Washington, D.C.: Pan American Health Organization. 963 pp.

Andrews, E. J., B. C. Ward, and N. H. Altman, eds. 1979. Spontaneous Animal Models of Human Disease. New York: Academic Press. Vol. I, 322 pp.; vol. II, 324 pp.

August, J. R. 1988. Dygonic fermenter-2 infections. J. Am. Vet. Med. Assoc. 193:1506-1508.

Bull, R. W., H. M. Vriesendorp, R. Cech, H. Grosse-Wilde, A. M. Bijma, W. L. Ladiges, K. Krumbacher, I. Doxiadis, H. Ejima, J. Templeton, E. D. Albert, R. Storb, and H. J. Deeg. 1987. Joint report of the Third International Workshop on Canine Immunogenetics. II. Analysis of the serological typing of cells. Transplantation 43:154-161.

Cornelius, C. E. 1969. Animal models—A neglected medical resource. N. Engl. J. Med. 281:934-944.

Deeg, H. J., R. F. Raff, H. Grosse-Wilde, A. M. Bijma, W. A. Buurman, I. Doxiadis, H. J. Kolb, K. Krumbacher, W. Ladiges, K. L. Losslein, G. Schoch, D. L. Westbroek, R. W. Bull, and R. Storb. 1986. Joint report of the Third International Workshop on Canine Immunogenetics. I. Analysis of homozygous typing cells. Transplantation 41:111-117.

Elliot, D. L., S. W. Tolle, L. Goldberg, and J. B. Miller. 1985. Pet-associated illness. N. Engl. J. Med. 313:985-995.

Finch, C. E., M. C. Pike, and M. Witten. 1990. Slow mortality rate accelerations during aging in some animals approximate that of humans. Science 249:902-905.

Fishbein, D. B., and L. E. Robinson. 1993. Rabies. N. Engl. J. Med. 329:1632-1638.

Gay, W. I. 1984. The dog as a research subject. The Physiologist 27:133-141.

Hegreberg, G., and C. Leathers, eds. 1980. Bibliography of Naturally Occurring Animal Models of Human Disease. Pullman, Washington: Student Book Corp. 146 pp.

Hubbert, W. T., McCulloch, W. F., and Schnurrenberger, P. R., eds. 1975. Diseases Transmitted from Animals to Man, 6th ed. Springfield: Ill: Charles C Thomas. 1,236 pp.

Ladiges, W. C., H. J. Deeg, R. F. Raff, and R. Storb. 1985. Immunogenetic aspects of a canine breeding colony. Lab. Anim. Sci. 35(1):58-62.

Minouchi, O. 1928. The spermatogenesis of the dog with special reference to meiosis. Jpn. J. Zool. 1:255-268.

NRC (National Research Council), Institute of Laboratory Animal Resources, Committee on Care and Use of Laboratory Animals. 1985. Guide for the Care and Use of Laboratory Animals. NIH Pub. No. 86-23. Washington, D.C.: U.S. Department of Health and Human Services. 83 pp.

Ostrander, E. A., P. M. Jong, J. Rine, and G. Duyk. 1992. Construction of small-insert genomic DNA libraries highly enriched for microsatellite repeat sequences. Proc. Natl. Acad. Sci. USA 89:3419-3423.

Ostrander, E. A., G. F. Sprague, Jr., and J. Rine. 1993. Identification and characterization of dinucleotide repeat $(CA)_n$ markers for genetic mapping in dog. Genomics 16:207-213.

Patterson, D. F., M. E. Haskins, P. F. Jezyk, U. Giger, V. N. Meyers-Wallen, G. Aguirre, J. C. Fyfe, and J. H. Wolfe. 1988. Research on genetic diseases: Reciprocal benefits to animals and man. J. Am. Vet. Med. Assoc. 193:1131-1144.

Patterson, D. F., G. A. Aguirre, J. C. Fyfe, U. Giger, P. L. Green, M. E. Haskins, P. F. Jezyk, and V. N. Meyers-Wallen. 1989. Is this a genetic disease? J. Small Anim. Pract. 30:127-139.

RCP (Registry of Comparative Pathology). 1972-1993. Handbook: Animal Models of Human Disease, fascicles 1-19. Washington, D.C.: Registry of Comparative Pathology. Available from RCP, Armed Forces Institute of Pathology, Washington, DC 20306-6000.

Sarmiento, U. M., and R. F. Storb. 1988a. Characterization of class II alpha genes and DLA-D region allelic associations in the dog. Tissue Antigens 32:224-234.

Sarmiento, U. M., and R. F. Storb. 1988b. Restriction fragment length polymorphism of the major histocompatibility complex of the dog. Immunogenetics 28:117-124.

Sarmiento, U. M., and R. F. Storb. 1989. RFLP analysis of DLA class I genes in the dog. Tissue Antigens 34:158-163.

Scott, J. P., and J. L. Fuller. 1965. Genetics and the Social Behavior of the Dog. Chicago: University of Chicago Press. 468 pp.

Shifrine, M., and F. D. Wilson, eds. 1980. The Canine as a Biomedical Research Model: Immunological, Hematological, and Oncological Aspects. Washington, D.C.: U.S. Department of Energy. 425 pp.

Stone, D. M., P. B. Jacky, and D. J. Prieur. 1991. The Giemsa banding pattern of canine chromosomes, using a cell synchronization technique. Genome 34:407-412.

Swindle, M. M., and R. J. Adams, eds. 1988. Experimental Surgery and Physiology: Induced Animal Models of Human Disease. Baltimore: Williams & Wilkens. 350 pp.

Teichner, M., K. Krumbacher, I. Doxiadis, G. Doxiadis, C. Fournel, D. Rigal, J. C. Monier, and H. Grosse-Wilde. 1990. Systemic lupus erythematosus in dogs: Association to the major histocompatibility complex class I antigen DLA-A7. Clin. Immunol. Immunopathol. 55:255-262.

Vriesendorp, H. M., H. Grosse-Wilde, and M. E. Dorf. 1977. The major histocompatibility system of the dog. Pp. 129-163 in The Major Histocompatibility System in Man and Animals, D. Götze, ed. Berlin: Springer-Verlag.

3

Husbandry

This chapter provides guidelines for the care of laboratory dogs. The first section, on housing, details design and construction considerations for facilities that house dogs, as well as for primary enclosures (here defined as cages and pens). The subsection on facilities contains information on buildings, rooms, and outside areas for containment of dogs, and that on environment and environmental control describes mechanisms for controlling the environment and gives the legislatively mandated ranges for temperature, humidity, and ventilation.

The remaining information in this chapter is supplemented by discussions in other parts of this report. For example, Chapter 4 ("Management of Breeding Colonies") contains sections on food for puppies and gestational or lactating dams and on record-keeping for a breeding colony that amplify the sections on food and identification and records in this chapter. Socialization of puppies is also discussed in Chapter 4. Modified primary enclosures and bedding for dogs with specific disorders are described in Chapter 6 ("Special Considerations").

The 1985 amendment to the Animal Welfare Act required the U.S. Department of Agriculture (USDA) to establish standards for exercise for laboratory dogs, and they were established in 1991. A federal court has now found that the regulations concerning exercise for dogs are inadequate and ordered that new regulations be written. This committee has reviewed the available information relevant to exercise, space, and well-being of dogs,

and it has found that, as was the case in 1985, it is inadequate to formulate objective standards.

Although knowledge of canine behavior is leading to a consensus that opportunities for social interaction with people, other dogs, or both are important for promoting canine well-being, no similar consensus is available concerning fitness and exercise. Another issue is the notion that a single standard can provide optimal care for all dogs. It is generally recognized that such factors as breed, physical conformation, age, health status, past experiences, and general behavioral characteristics influence what constitutes adequate space and exercise. For example, a dog undergoing a surgical procedure might require a restricted space to limit its activity. Once the dog has recovered from the surgical procedure, a different space and exercise regimen can be implemented. Likewise, the space and type and duration of exercise required for Alaskan sled dogs in working condition is quite different from that required for Shih Tzu and other brachycephalic breeds. Finally, medical research benefits from the availability of dogs with inherited disorders similar to those of humans, and the presence of these disorders in dogs imposes the same types of restrictions that human patients must endure. Unsupervised exercise is often contraindicated in dogs with heart and metabolic diseases. Similarly, the construction and layout of primary enclosures for dogs with such conditions as muscular dystrophy, bleeding disorders, blindness, or Ehlers-Danlos syndrome must be carefully considered to avoid compromising their health and well-being.

The most important objective for those responsible for housing dogs should be to achieve an overall high level of care, rather than to conform rigidly to specific standards. Animal well-being must be assessed case by case by those qualified to do so. The regular evaluation of animal well-being is an important aspect of any husbandry and animal-care program and serves as a measure of the appropriateness of animal-care procedures. Procedures that are ultimately linked to the well-being of the individual are defined as performance standards. The committee strongly recommends that performance standards, coupled with sound professional judgment, be used to develop space requirements and exercise programs for dogs. This committee is firmly convinced that performance standards are ultimately better for each dog's physical and behavioral well-being than engineering standards, which might lack the flexiblity necessary to meet the needs of all dogs.

HOUSING

Facilities

Housing facilities for dogs must be designed and constructed so that they are structurally sound, protect animals from injury, contain animals

securely, and prevent entry of other animals (9 CFR 3.1a). Dog facilities vary in size and complexity, depending on their purpose (e.g., holding or breeding), colony size and type (e.g., specific-pathogen-free or conventional), and breed. The design of breeding facilities should address the following:

- The design should facilitate the conduct of research.
- There should be sufficient space for expansion, both for adding animals and for increasing ancillary operations.
- Breeding facilities should have sufficient space to house dams with litters and the progeny.
- The design should promote effective sanitation and husbandry procedures.
- Operation of the facility should be efficient and cost-effective.
- Construction should be economical.

The physical facilities and equipment should be constructed and operated to fulfill the following criteria:

- Contamination from areas adjacent to, but not part of, the facility should be minimized. The locations of equipment washing and sterilizing, food and bedding storage, quarantine, treatment, receiving and shipping, shipping-crate storage, mechanical services, shops, offices, and laboratories should minimize crossovers from soiled or contaminated to clean areas. Clean material and equipment should not come into contact with soiled and contaminated material and equipment.
- There should be sufficient control of temperature, humidity, ventilation, and lighting to provide the animals with appropriate conditions for their comfort and well-being.
- Behavioral well-being should be considered by allowing for visual contact between dogs, social housing, exercise areas, and other appropriate areas.
- The entry of vermin should be prevented.
- Provisions should be made for lunchrooms, locker rooms, and toilets for animal-care personnel.
- Caging equipment and feeding and watering devices should provide a safe environment, make food and water readily available, minimize the opportunity for transmission of diseases and parasites, and make sanitation and sterilization efficient.
- Auxiliary equipment—such as washing machines, cage racks, rolling equipment (e.g., dollies, tables, and carts), and fixed equipment (e.g., cabinets, sinks, and shelving)—should be designed, fabricated, and used to promote maximal sanitation and operating efficiency.

When a dog facility is designed to be part of a larger facility housing other species of animals or part of a multipurpose building with offices and research laboratories, the physical relationships between areas must be carefully planned (NRC, 1985a). Those establishing operating procedures should use the best available information on physiology; nutrition; genetics; behavior; animal breeding, care, and maintenance; colony management (production and research); and disease control.

Dogs can be housed in indoor facilities, outdoor facilities, or a combination of the two (sheltered housing facilities). If the site is exclusively indoors, the only factors that influence site selection are local zoning regulations, the ability to control odors and noise, the availability of appropriate utilities (e.g., sewerage and water) (9 CFR 3.1d), and the proximity to other businesses. Indoor facilities should be constructed and maintained in compliance with CFR, Title 9, Part 3.2 and the *Guide* (NRC, 1985a), as summarized below.

Indoor Facilities

Walls. Exterior walls should be fire-resistant and impervious to vermin. To facilitate cleaning, interior walls should be smooth, hard, and without pits or cracks, and they should be capable of withstanding the impact of water under high pressure and scrubbing with cleaning agents (e.g., detergents) and sanitizing agents (e.g., disinfectants). They should be protected from damage caused by movable equipment.

Ceilings. Ceilings should be smooth, moistureproof, and free of imperfect junctions. Surface materials should be capable of withstanding scrubbing with detergents and disinfectants. Exposed pipes and fixtures are undesirable.

Floors. Floors can be constructed of a variety of materials that are smooth, moistureproof, nonabsorbent, and skidproof; that are resistant to wear and the adverse effects of detergents, disinfectants, acid, and solvents; and that are able to support heavy equipment without being gouged, cracked, or pitted. They should also be easy to clean.

Drainage. Drainage must be adequate to allow rapid removal of water (9 CFR 3.1f). If floor drains are used, they should be constructed and maintained in accordance with the *Guide* (NRC, 1985a). Rim flush drains should be at least 6 in (15.2 cm) in diameter. Porous trap buckets installed in the drains aid in cleaning and screen out solid waste. Floor drains must contain traps that prevent backflow of sewage and gases (9 CFR 3.1f). If

unused floor drains are present, they should be closed with gastight seals that are flush with the floor surface.

Doors. All rooms should have doors. External doors should have adequate latches and locks and should be verminproof when closed. If they are left open during warm weather, adequate screening is essential. All door frames should be sealed to walls and partitions with caulking compound or a similar material.

Ports in animal-room doors allow personnel to observe the dogs without entering the rooms, prevent injury to personnel while they are opening doors, and provide a way to verify that room lights are on at appropriate times. Experience has shown that doors at least 42 in (107 cm) wide and 84 in (213 cm) high allow free passage of cages and equipment. The doors should be equipped with locks and kickplates and should be self-closing.

Outside windows. Outside windows and skylights might not be desirable, because they can contribute to unacceptable variations in temperature and photoperiod. Other problems associated with outside windows and skylights include dust and bacteria buildup on frames, drafts, and increased ventilation costs.

Washrooms and sinks. Washing facilities for personnel (e.g., basins, sinks, or showers) must be provided and must be readily accessible (9 CFR 3.1g).

Sheltered Housing Facilities

A sheltered housing facility, as defined by the Animal Welfare Regulations (AWRs), is a facility that provides shelter, protection from the elements, and protection from temperature extremes at all times (9 CFR 1.1). It can consist of runs or pens in a totally enclosed building or indoor-outdoor runs with the indoor runs in a totally enclosed building. The requirements for the sheltered portion of such facilities are identical with those for indoor facilities, with the additional stipulation that the shelter structure must be large enough to permit each animal to sit, stand, and lie down in a normal manner and to turn around freely (9 CFR 3.3).

The outdoor portion of a sheltered housing facility should be constructed to prevent the introduction of vermin. Outdoor floor areas in contact with animals should be constructed of hard, moisture-resistant material and be properly drained. The use of compacted earth, sand, gravel, or grass is discouraged. The sides of runs can be constructed of chain-link fencing and steel posts or pipe frames or, when necessary to prevent fighting or injury, of solid concrete block coated with sealant. Fencing at the lower ends of

runs and pens should be high enough above the surface to permit adequate drainage but not high enough to allow young puppies to escape. Curbs at least 6 in (15.2 cm) high should be constructed between runs to help prevent the spread of microorganisms during washing. Curbs 24-30 in (61.0-76.2 cm) high might be necessary in runs in which the dog population is constantly changing. Higher curbs might be beneficial in whelping-pen runs to reduce the anxiety of nursing bitches. Run doors or gates should have well-made latches that can be easily opened by animal-care personnel but not by the dogs. Special consideration must be given to removing animal wastes and controlling noise.

Outdoor Facilities

The AWRs, with some restrictions, permit facilities to house dogs solely outdoors, provided that each animal has access to a structure (consisting of a roof, four sides, and a floor) that furnishes adequate protection from cold, heat, the direct rays of the sun, and the direct effects of wind, rain, and snow (9 CFR 3.4). In general, this type of housing is discouraged for dogs being used in an experimental protocol, because environmental factors, infectious agents, and vermin are difficult to control. In other instances (e.g., in protocols requiring acclimation or in breeding colonies maintained in temperate climates), outdoor facilities might be adequate.

Environment and Environmental Control

An important part of maintaining the health and well-being of laboratory animals is control of the environment. In nature, animals respond to environmental changes both behaviorally and physiologically in a manner that will maintain homeostasis. In an animal room, a behavioral response might not be possible, and the animal must deal with an altered environment physiologically. Therefore, it is necessary to control the environment to avoid physiologic changes. Besch (1985) has reviewed environmental factors that can effect the biologic responses of laboratory animals.

Temperature and Humidity

Temperature and humidity are important considerations in a dog facility (Besch, 1985). Dogs can tolerate moderate ranges of temperature and weather, provided that they have appropriate amounts of food and water, have access to shelter, and are allowed sufficient time to acclimate to their environment. The *Guide* recommends that room temperature for dogs be maintained within a range of 18-29°C (64.4-84.2°F) and relative humidity within a range of 30-70 percent. The AWRs require that the ambient temperature in indoor

facilities not fall below 7.2°C (45°F) or rise above 29.4°C (85°F) for more than 4 consecutive hours when dogs are present (9 CFR 3.2a). Except as approved by the attending veterinarian, ambient temperature must not fall below 10°C (50°F) for dogs not acclimated to lower temperatures, breeds that cannot tolerate lower temperatures, and young, old, sick, or infirm dogs (9 CFR 3.2a).

Dogs recovering from general anesthesia are frequently hypothermic. Every attempt should be made to maintain normal body temperature during surgery and recovery. This can be accomplished by using supplemental sources of heat (e.g., heating pads and heat lamps), by avoiding direct contact with heat-conducting surfaces (e.g., metal), and by maintaining the postoperative recovery cage at 27-29°C (80.6-84.2°F) (NRC, 1985a). Newborn pups have poorly developed thermoregulatory mechanisms and might require supplemental sources of heat. Temperatures of 29.4-32.2°C (85-90°F) have been suggested for the first week of life (Poffenbarger et al., 1990).

Each room should be provided with temperature controls and high- and low-temperature alarms. Graphic recorders are useful for monitoring system performance. Ideally, the temperature controls should allow individual adjustments in dry-bulb temperature of ± 1°C (± 2°F) within the range of 18.3-29.4°C (65-85°F).

Relative humidity should be maintained at 30-70 percent throughout the year (NRC, 1985a). It is important to control sources of humidity, such as cage-cleaning equipment, transient loads from cleaning water (Gorton and Besch, 1974), and thermal and mass loads from animals (Besch, 1991). Low humidity can contribute to respiratory distress; and coughs, pneumonitis, and other problems can follow. High humidity impairs efficient body-cooling (Besch, 1991).

Ventilation

Ventilation serves multiple functions. It supplies oxygen; removes heat generated by animals, lights, and equipment; dilutes gaseous contaminants; and helps to control the effects of infiltration and exfiltration (Clough and Gamble, 1976; Edwards et al., 1983). Gorton et al. (1976) have reported a method for estimating laboratory animal heat loads.

Indoor facilities must be sufficiently ventilated when dogs are present to provide for their comfort and well-being and to minimize odors, ammonia concentrations, drafts, and moisture condensation. Auxiliary ventilation must be provided when the ambient temperature is 29.5°C (85°F) or higher (9 CFR 3.2b). It is commonly thought that 10-15 volumetric changes per hour with outside air must be provided to animal rooms and that air must not be recirculated. As a consequence, animal facilities are generally venti-

lated with "one-pass" air, although the *Guide* (NRC, 1985a) includes provisions for alternative methods of providing equal or more effective ventilation. Besch (1992) has reviewed alternative methods of ventilation.

Ventilation system design and construction considerations include the following:

- Diffusers and exhaust openings should be located and controlled to prevent drafts.
- Outside openings and exhaust-ventilation grillework should be screened to prevent entry of vermin. Screening should be cleaned regularly.
- Air pressure in clean areas and animal rooms should be greater than that in public and refuse areas. Where pathogenic organisms are present, a negative-pressure system is necessary.
- Ventilating mechanisms should be equipped with suitable alarm systems that will be activated if the temperature moves outside the desired range or if power fails.
- Supplemental exhaust fans or exhaust systems increase drying and reduce humidity when fixed equipment is being washed. If such systems are used, they should be permanently mounted in external windows or wall openings, their frames should be sealed to the building structure, and the systems should be screened.
- Emergency power sources should be available in case of power failure.

Power and Lighting

Electric systems should be safe, furnish appropriate lighting, and provide a sufficient number of outlets. Lighting systems should allow for either manual or timer-controlled changes in illumination levels or photoperiods, and timer performance should be checked regularly. Lighting fixtures, switches, and outlets should be sealed to prevent entry or harboring of vermin. Moistureproof switches and outlets should be installed where water is used in cleaning. Emergency power should be available.

Illumination must be adequate and uniformly diffuse throughout each animal room to allow proper cleaning and housekeeping, to permit inspection of animals, and to maintain the animals' well-being (9 CFR 3.2c). Light levels of 323 lx (30 ft-candles), measured 1.0 m (3.3 ft) above the floor, appear to provide sufficient illumination for routine animal care (Bellhorn, 1980; NRC, 1985a). A regular diurnal lighting cycle must be provided (9 CFR 3.2c).

Noise Control

Barking dogs can be a nuisance both to personnel working in animal facilities and to the adjacent population. Self-generated noise of 80-110 dB (Peterson, 1980; Sierens, 1976) has been measured in dog rooms. The effects of noise on animals are reviewed in the *Guide* (NRC, 1985a).

Noise-control measures should be implemented in both indoor and outdoor environments. Sound transmission can be reduced by using concrete to build walls, covering concrete walls with sound-attenuating material, and eliminating windows (NRC, 1985a). Pekrul (1991) has discussed other means of decreasing noise in animal facilities. Sound-attenuating materials may be bonded to walls or ceilings only if they can be sanitized and will not harbor vermin. Outdoor runs must be designed and constructed to comply with local noise ordinances.

Chemicals and Toxic Substances

Many of the chemicals used in animal facilities for cleaning, sanitizing, pest control, and other purposes can be toxic to housed animals and personnel. In addition, some materials used in construction for coating surfaces can react with certain cleaning and sanitizing agents to produce toxic gases, including chlorine. Where possible, the use of chemicals should be avoided. For example, adequate ventilation is more effective than chemicals in eliminating most animal-room odors, provided that air inlets are not placed near the building exhaust. Newberne and Fox (1978) and Besch (1990) have reviewed chemicals and other toxicants found in animal facilities.

Where chemical agents must be employed, it is essential to be familiar with their potential toxicity and to develop procedures for using and disposing of them properly. Noxious chemicals should not be used to clean animal facilities. Adequate rinsing is essential to prevent the skin irritation or allergic reactions that can be caused by some cleaning and sanitizing agents (e.g., pine oil).

Primary Enclosures

Primary enclosures should facilitate research while maintaining the health and well-being of the dogs. They must confine dogs securely, enable them to remain clean and dry, protect them from injury, and contain sufficient space to allow them to sit, lie, stand, turn around, and walk normally (9 CFR 3.6a). The design should allow inspection of cage or pen occupants without disturbing them and provide easy access to feeding and watering devices for filling, changing, cleaning, and servicing.

Cages or pens should be fabricated of smooth, moisture-impervious, corrosion-resistant materials that can be easily sanitized and sterilized. Floors must be constructed to preclude entrapping toes, dew claws, or collars. Expanded metal or plastic-covered metal mesh is satisfactory for pens or runs, provided that the dogs' feet cannot pass through the openings (9 CFR 3.6a2x). Pen floors must have adequate drainage.

Each cage and pen should have a hinged or sliding door that covers the opening sufficiently to prevent escape of the occupants. Each door should have a latch that holds the door securely closed.

Space Recommendations

The AWRs require that the floor space for each dog equal at least the "mathematical square of the sum of the length of the dog in inches (measured from the tip of its nose to the base of its tail) plus 6 inches [15.24 cm]," expressed in square feet (9 CFR 3.6c1i). In addition, the interior height of each enclosure must be "at least 6 inches [15.24 cm] higher than the head of the tallest dog in the enclosure when it is in a normal standing position" (9 CFR 3.6c1iii). Each bitch with nursing pups must be given additional floor space based on breed and behavioral characteristics and in accordance with generally accepted husbandry practices, as determined by the attending veterinarian (9 CFR 3.6c1ii). The additional space for each nursing pup must be at least 5 percent of the minimum required for the bitch, unless otherwise approved by the attending veterinarian (9 CFR 3.6c1ii). Minimal space recommendations for dogs are also given in the *Guide* (NRC, 1985a, p. 14). These requirements and recommendations are based primarily on professional judgment and convention.

The few scientific studies on this subject have focused on how enclosure size affects movement, activity patterns, and physical fitness. Clark et al. (1991) found no decreases in physical fitness, as measured by heart rate and muscle enzyme (succinate dehydrogenase) activity, when dogs were housed in cages or runs of various sizes that complied with federal standards and guidelines; however, modest decreases in fitness were found when dogs were housed in cages smaller than mandated by the AWRs. It has been shown that, in general, dogs are more active in pens and runs than in cages; however, dogs housed in the largest enclosures are not always the most active (Hetts et al., 1992; Hite et al., 1977; Hughes and Campbell, 1990; Hughes et al., 1989; Neamand et al., 1975). Enclosure size has not been demonstrated to affect the musculoskeletal system (Newton, 1972), cortisol concentrations (Campbell et al., 1988; Clark et al., 1991), or selected measures of immune function (Campbell et al., 1988). Although they provide interesting and relevant information, the studies do not provide

sufficient objective, scientific data on which to base space requirements for dogs.

To set standards based on scientific data, one must show a correlation between cage size and behavioral well-being. That poses two problems: it is not clear how to define and measure behavioral well-being, and the determination of well-being depends on human interpretations of the data. Movement and activity patterns are unlikely to be sensitive behavioral measures, because a dog's activity can be increased without improving its well-being (e.g., if there is locomotor stereotypy or increased activity caused by social isolation or competition for space). Moreover, the definition of movement varies between studies, so it is difficult to compare and interpret results. It is generally accepted that a variety of perspectives are needed to assess well-being, including measures of physical health, of neuroendocrine and immunologic responses to stress, of the ability to respond effectively to social and nonsocial environments, and of behavior. Scientific data on dogs are inadequate to support any such assessment relative to enclosure size.

EXERCISE AND ENVIRONMENTAL ENRICHMENT

The requirements for providing opportunities for dogs to exercise are specified in the AWRs (9 CFR 3.8). The following paragraph summarizes the AWRs now in effect. It is incumbent on the reader to keep abreast of changes that might occur as the result of further federal court or USDA actions.

Dogs over 12 weeks old, except bitches with litters, must be given the opportunity for regular exercise if they are kept individually in cages, pens, or runs that are less than 2 times the AWR-required floor space. Dogs housed in groups do not require exercise periods, provided that the total floor space of the cages, pens, or runs equals the sum of the AWR-required spaces for the dogs if housed individually. If a dog is housed without sensory contact with other dogs, it must receive positive physical contact with humans at least once a day. Forced-exercise programs (e.g., swimming or walking on treadmills or carousel devices) are not considered to comply with the AWRs. Each institution is responsible for developing a plan for providing exercise. The plan must be approved by the attending veterinarian and must be made available to USDA on request. Exceptions to the requirement for exercise can be made by the attending veterinarian case by case or, if exercise is inappropriate for a scientific protocol, by the institutional animal care and use committee (IACUC). In the former instance, the exemption from exercise must be reviewed every 30 days, unless it was granted because of a permanent condition (9 CFR 3.8d). In the latter instance, exemptions must be reviewed at appropriate intervals, as determined by the IACUC, but not less often than every 6 months (9 CFR 2.31)

Recent studies have provided some information on exercise and well-being. Clark et al. (1991) and Hetts et al. (1992) found that 30 minutes of forced treadmill exercise five times a week did not affect physical fitness or behavior as measured in the study. Campbell et al. (1988) reported that releasing dogs either singly or as a group into a large area for 35-minute exercise periods three times a week did not affect cage activity patterns or weekly measures of selected hematologic or serum biochemical values. However, dogs were more active during the release periods than in their cages, and dogs released individually had different activity patterns from those of dogs released in groups. Studies on enclosure size and exercise are cited in the section above on space recommendations. Although the studies have provided important and relevant information, sufficient data are still not available to support definitive conclusions about the relationship between exercise and well-being. Future studies should be based on larger samples, use a variety of behavioral measures to evaluate well-being (activity patterns are not likely to be sensitive indicators of well-being), and consider the substantial individual variations in physiologic characteristics that have been reported.

It is well known that dogs are highly social animals, and social isolation and solitary housing are considered to be important stressors of social species (Wolfle, 1990). Solitary housing has been shown to be associated with less activity and with nonsocial repetitive behaviors (Hubrecht et al., 1992). Hetts et al. (1992) have found that socially isolated dogs (i.e., dogs having only auditory contact with other dogs and contact with people only during routine husbandry procedures) display bizarre movement patterns and tend to vocalize more than dogs that have more social contact. Several studies have reported that dogs are more active in the presence of humans (Campbell et al., 1988; Hetts et al., 1992; Hughes and Campbell, 1990; Hughes et al., 1989), especially when human presence is relatively rare (Hubrecht et al., 1992). It has also been shown that dogs housed in pairs sleep more than dogs housed singly (Hetts et al., 1992). Although the relationship between sleep patterns and well-being has not been studied in dogs, there is evidence in other species that normal sleep can be disrupted by a variety of environmental stressors and that return to normal sleep patterns can be a sensitive indicator of an animal's adaptation to environmental changes (Ruckenbusch, 1975).

Evidence of the importance of social interactions for dogs is strong enough to support a recommendation that dogs be socially housed in compatible groups, be given opportunities for social interaction during the exercise period, or both. The AWRs address the compatible grouping of dogs in the same primary enclosure (9 CFR 3.7). Age, sex, experience, and genetic differences in social behavior between individuals and breeds influence how dogs accept social housing and respond to social interaction (Fuller, 1970;

King, 1954; Scott and Fuller, 1965). Social interactions should minimize fearful and aggressive behaviors.

Examples of plans that provide social interactions are leash walking and release of dogs in an enclosed area for specified periods. In the latter, several compatible dogs that are housed in the same room can be released together; however, females in proestrus or estrus should not be released with males. Exercise rooms should be cleaned and sanitized between uses by dogs from separate rooms to minimize disease transmission. Only dogs of similar microbiologic status should be combined in groups (see Chapter 5).

If dogs are to be group-released, the composition of the group should remain as stable as possible (i.e., the members of the group should be the same dogs each time), because how readily a group of dogs accepts new members varies a great deal. Some dogs form closed social groups and attack new members (King, 1954). Changes in group composition often cause instability in the social dominance hierarchy, which in turn can result in intraspecific aggression. It is important to remember that two dogs make a pack, and the behavior of a pack is often very different from that of an individual dog. A thorough understanding of pack structure and social behavior is important for those managing research dogs. Any dog that is being attacked or threatened by the group to the extent that it cannot move about freely should be removed and given an alternative method of exercise. Group-released dogs should be observed frequently during the exercise period to ensure their safety.

Positive social interactions with humans can be achieved by having one or more people in the room during the exercise period. There is evidence that passive contact with a person is more reinforcing to dogs that have been socially isolated than is active contact (Stanley, 1965; Stanley and Elliot, 1962). If a dog displays fearful behavior when handled or petted, the handler should sit passively, avoid eye contact, and allow the dog to approach at will. As fearful behavior decreases, contact can gradually become more active.

Information on other types of environmental enrichment for dogs is scarce. The need for complex or varied environments has not been studied. Dogs have been observed to manipulate and direct attention to loose objects they find in their enclosures (Hetts et al., 1992), and dogs provided with toys spent an average of 24 percent of their time using them (Hubrecht, 1993). The toys reduced the dogs' inactive time and decreased destructive behavior aimed at cage apparatuses (Hubrecht, 1993). The relevance of these behavioral changes to well-being is not yet known. Nonetheless, such devices as balls, chew toys, and ropes might be considered for dogs in restricted environments. It is recommended that an ethologist, comparative psychologist, or animal behaviorist knowledgeable about dog behavior be

consulted by those designing exercise and social interaction plans or when other questions arise concerning the behavioral well-being of dogs.

FOOD

Selecting Optimal Rations

Many commercially available dog foods contain all essential nutrients in their required proportions, as outlined in *Nutrient Requirements of Dogs* (NRC, 1985b) and the Association of American Feed Control Officials' *Official Publication 1993* (AAFCO, 1993). These foods are manufactured in dry, semimoist, and canned forms. Dogs should be fed only complete and balanced diets. Specific procedures should be followed to ensure that stored foods do not become deficient in nutrients (NRC, 1985a).

Diet quality can be evaluated by examining the label for a statement of nutritional adequacy, which must be present on all dog-food products sold across state lines. This statement informs the purchaser whether the product has been approved for use as a complete ration for specified life stages (i.e., growth, maintenance, or pregnancy and lactation). Approval is obtained by one of the following means:

- Each of the diet's individual ingredients is analyzed for all essential nutrients; the sum of these nutrients in all ingredients must meet or exceed the nutritional requirements of the animal for specified life stages.
- The product itself is chemically analyzed and shown to meet or exceed the essential-nutrient requirements for specified life stages.
- The product passes a feeding trial as specified by the Association of American Feed Control Officials.

If the product fails to be approved, it must be labeled for use as a dietary supplement only and is not appropriate for use as a dog food. Of the three means of approval, only the feeding trial evaluates the availability of the nutrients in the product. Dog foods approved by that method should be used whenever possible. If such a diet cannot be used, because it would interfere with the experimental design (e.g., nutritional studies with purified diets), the manufacturer of the diet to be used should be consulted about experience with the diet's performance under given conditions.

Many commercially available dog foods, although designed for a specified life stage, are approved and adequate for use during all life stages. Most growth formulations will meet the requirements for gestation, lactation, and maintenance. Similarly, most gestation-lactation products also meet requirements for growth and maintenance. Some foods intended for maintenance will meet the criteria for more than one life stage. However,

no food should be used for growth, gestation, and lactation unless its label states that it meets or exceeds nutrient requirements for these life stages.

Special therapeutic diets are available for dogs with specific nutrient requirements caused by the presence of disease (Kirk and Bonagura, 1992; Lewis et al., 1987). Such diets should be fed only under the supervision of a veterinarian.

Feeding

Most commercial rations are formulated to meet all nutrient requirements if a dog eats enough to fulfill its caloric requirements. Estimates of daily caloric requirements can be obtained from several sources, including the manufacturer of the specific food being used. These estimates can be used to initiate feeding programs, but they might need substantial modification because of variations in metabolic rates of individual dogs.

Under most kennel conditions, meal feeding is preferable to free-choice feeding, and individual feeding is preferable to group feeding for the following reasons:

- Restricted feeding has been shown to decrease the incidence of metabolic bone disease in growing dogs that mature at greater than 30 lb (Kealy et al., 1992).
- Restricted feeding has been shown to decrease the incidence of obesity in young beagles and Labrador retrievers (Kendall and Burger, 1980).
- The continual ingestion of small amounts of food observed in free-choice feeding programs stimulates oral bacterial growth and might promote dental disease and gingivitis (Dr. John Saidla, Department of Clinical Sciences, New York State College of Veterinary Medicine, Cornell University, Ithaca, N.Y., unpublished).
- When dogs are fed in groups, dominant dogs might overeat and might prevent subordinate dogs from eating enough to fulfill their daily needs.
- When dogs are fed individually, their food intake can be monitored.

Some kennels have successfully used free-choice feeding to maintain dogs. This practice is most successful when the diet used is a food of relatively low energy density and palatability.

Dogs must be fed at least once a day, except as required for adequate veterinary care (9 CFR 3.9a). Each healthy adult dog should be fed enough to maintain its optimal body weight; this amount will vary with the environment and with the dog's age, sex, breed, temperament, and activity. Within an individual breed, there is often a wide variety of *normal* sizes. It is better to evaluate a dog's size according to how it looks and how it feels than according to body weight alone. With the hands-on approach, a dog's

rib cage, spinous processes, and ileal wings should be easily palpable. They should not protrude from under the skin, nor should they be buried under a layer of adipose tissue. Once an adult dog is being maintained at its ideal body size, its weight can be used as a reference for future evaluation of food requirement. However, the loss of muscle mass and gain of adipose tissue, such as are observed in several endocrine disorders, and shifts in fluid balance might make body weight an inaccurate means of assessing nutritional status; therefore, body weight should not completely replace appearance and feel as assessment methods.

Contaminants

Animal-colony managers should be judicious in purchasing, transporting, storing, and handling food to ensure that it does not introduce diseases, potential disease vectors, or parasites. Food must be stored in a manner that prevents spoilage, contamination, and vermin infestation. Open bags must be stored in leakproof containers with tightly fitting lids (9 CFR 3.1e; NRC, 1985a).

Contaminants in food can have dramatic effects on biochemical and physiologic processes. In general, food for dogs should not be manufactured or stored in facilities used for farm foods or any products containing additives, such as rodenticides, insecticides, hormones, antibiotics, fumigants, or other potential toxicants.

WATER

Ordinarily, all dogs should receive fresh, clean, potable water ad libitum. If water is not continuously available, the AWRs require that it be made available at least twice a day for at least 1 hour each time, unless it is restricted by the attending veterinarian (9 CFR 3.10).

Watering devices can be either portable or self-watering. Self-watering devices are convenient and reduce labor, but they require scheduled observations to ensure proper function. Portable watering devices should be easily removable for daily rinsing and periodic sanitizing.

BEDDING AND RESTING APPARATUSES

Bedding can be used in some husbandry situations. For example, if drains are not available, it can be used as an absorbent to help to keep dogs clean and dry. Kinds of bedding typically used for dogs are wood shavings and shredded paper. Bedding must be stored in a manner that protects it from contamination and vermin infestation (9 CFR 3.1e).

Resting apparatuses, especially those made of high-density polyethyl-

ene (Britz, 1990), are useful for minimizing loss of body heat from dogs in postoperative recovery, dogs in ill health, and young pups with poorly developed heat-control mechanisms.

SANITATION

The schedule for cleaning and disinfecting dog facilities will vary according to the physical makeup of pens, cages, or runs and other factors. Generally, primary enclosures should be cleaned as needed and sanitized at least once every 2 weeks. Excrement pans and runs should be cleaned daily. If pens and runs composed of materials that cannot be sanitized (e.g., gravel, sand, or pea stone) are used, the contaminated materials should be replaced as often as necessary to prevent odors, diseases, and vermin infestation. Procedures outlined in the AWRs (9 CFR 3.11) should be followed. Dogs must be removed before the floors of primary enclosures are thoroughly cleaned. Primary enclosures containing bitches near parturition, dams with litters, or dogs in quarantine require a cleaning schedule that disturbs them as little as possible.

Equipment and peripheral areas should be cleaned according to the recommendations of the *Guide* (NRC, 1985a). Waste should be removed regularly and frequently, and safe, sanitary procedures should be used to collect and discard it (NRC, 1985a).

IDENTIFICATION AND RECORDS

Identification

Each dog held in a research facility must be marked either with the official USDA tag or tattoo that was on the dog at the time it was acquired or with a tag, tattoo, or collar applied by the facility that individually identifies the dog by number (9 CFR 2.38g1).

Unweaned puppies need not be individually numbered as long as they are maintained in the same primary enclosure as their dam (9 CFR 2.38g3). However, they can be marked for identification with a variety of methods. Colored yarns or spots made with such marking substances as nail polish or paint provide a quick visual reference. Subcutaneous dots can be made by injecting a small amount of tattoo ink beneath the abdominal skin with a tuberculin syringe and 25-gauge needle. Ink dots should be placed in a different location for each pup (e.g., left axilla and right side of abdomen). The location or pattern of the dots and the sex and markings of each pup provide individual identification until permanent tattoos can be applied.

Tattooing of the inner surface of a dog's ear is common. Before the tattoo is applied, the ear should be cleaned thoroughly. Tattoos can be

applied with special pliers or an electrovibrator. A tattoo might have to be reapplied after several years. An ancillary method for individually identifying dogs uses a subcutaneously implanted, permanently encoded microchip (transponder) that, when activated by an electronic scanner, broadcasts the encoded number; the scanner transfers the broadcast to a processor that produces either a digital readout or a printed copy. This identification system can be useful during daily examination of dogs being used in studies, but it has not been approved by USDA as the sole source of identification because there is no standard implantation site, no standardized scanner, and no definitive information on whether the microchip migrates from the implantation site. USDA has approved the trial use of the microchips for a few commercial organizations (Richard L. Crawford, Assistant Deputy Administrator for Animal Care, Regulatory Enforcement and Animal Care, APHIS, USDA, Beltsville, Md., personal communication, 1993).

Record-Keeping

Record-Keeping for Scientists and Animal-Care Staff

A life-long, day-to-day log of individual events and experimental procedures experienced by each dog—especially surgery, postsurgical analgesia, and other veterinary interventions—should be carefully maintained. The log will assist animal-care personnel in providing appropriate care, investigators in interpreting research results, and the institution in preparing its annual report to USDA (9 CFR 2.36). Computer programs for maintaining such logs are commercially available (Riley and Blackford, 1991). For small colonies, hand-kept records on each dog might be more appropriate. McKelvie and Shultz (1964) described a record system for long-term studies that is still relevant; it covers clinical examination and includes a coded daily log entry of all events that the animal has experienced.

Records Required by Federal Regulations

Research facilities are obliged to maintain records on procurement, transport, and disposal of all dogs and an inventory of dogs in the facility. When dogs are procured, facilities are required to obtain detailed information on the seller—including name, address, USDA license or registration number or vehicle license number and state—and a description of each dog (9 CFR 2.35b). Likewise, when a dog is transferred to another owner, records must include the name and address of the purchaser, the date and method of transport, and a certificate of health (9 CFR 2.35c). Additional information is available in the section of this chapter entitled "Transportation."

A variety of forms are available to assist institutions in keeping records.

Among them are USDA Interstate and International Certificate of Health Examination for Small Animals (VS Form 18-1), Record of Dogs and Cats on Hand (VS Form 18-5), and Record of Disposition of Dogs and Cats (VS Form 18-6). These forms can be obtained from Regulatory Enforcement and Animal Care, APHIS, USDA, Federal Building, Room 565, 6505 Belcrest Road, Hyattsville, MD 20782 (telephone: 301-436-7833). All records should be maintained for at least 3 years (9 CFR 2.35f).

Records must also be maintained on all offspring born to dogs in the colony (9 CFR 2.35b) and on exceptions to the requirements for exercise (9 CFR 3.8d). Facilities conducting research on any vertebrate animal, including dogs, are obliged to maintain additional records that include the following:

- minutes of meetings of the IACUC;
- semiannual IACUC reports;
- protocols involving animal use;
- scientifically justified deviations from the AWRs; and
- studies involving pain in which analgesics cannot be used.

Some of the information must be reported annually to USDA (9 CFR 2.36); other information, such as approved protocols, must be maintained for 3 years after the study ends (9 CFR 2.35f).

EMERGENCY, WEEKEND, AND HOLIDAY CARE

Dogs should be observed and cared for by qualified personnel every day, including weekends and holidays, as outlined in the *Guide* (NRC, 1985a). Emergency veterinary care should be available after working hours and on weekends and holidays. For dogs undergoing particular experimental procedures and dogs with conditions that might require emergency care, investigators should develop written protocols and provide appropriate additional coverage.

TRANSPORTATION

Transportation over long distances is known to be a stressor for animals. Proper attention to environmental conditions, cage design, and care in transit will minimize the stress. The AWRs specify the requirements for transporting dogs (9 CFR 3.13-3.19). Before a dog is transported, special arrangements must be made between the shipper (consignor), the carrier(s) or intermediate handlers, and the recipient (consignee). The shipper must certify that the dog was offered food and water during the 4 hours before delivery to the carrier and must prepare a written certification, which must

be securely attached to the cage and must contain the shipper's name and address, the animal identification number, the time and date when the dog was last offered food and water, specific instructions for feeding and watering the dog for a 24-hour period, and the signature of the shipper with the date and time when the certification was signed.

Primary Enclosures

Carriers must not accept dogs for shipment if their primary enclosures do not meet the requirements of the AWRs (9 CFR 3.14). The primary enclosure must be large enough to allow a dog to turn around while standing, to stand and sit erect, and to lie in a natural position. Primary enclosures must be structurally sound, free of internal protrusions that could cause injury, constructed of nontoxic materials, and able to withstand the normal rigors of transportation. The container must secure the animal and all parts of its body inside the enclosure. Devices, such as handles, must be attached to the outside to allow the container to be lifted without tilting. The container must have a leakproof, solid floor or have a raised floor and a leakproof collection tray. If animals are housed directly on the floor, absorbent bedding material must be provided. Primary enclosures must be cleaned and any litter replaced if dogs are in transit for more than 24 hours. Primary enclosures should be well ventilated to minimize the potential for a thermal gradient during shipment. Additional specifications for transport cages are in the AWRs (9 CFR 3.14) and the *IATA Live Animal Regulations* (IATA, 1993 et seq.).

Puppies 4 months old or younger must not be transported in the same primary enclosure with adult dogs other than their dams. For puppies shipped during sensitive periods of behavioral development (i.e., 8-14 weeks of age; see Scott and Fuller, 1965), shipping stress should be minimized. Dogs likely to display aggressive behavior must be shipped individually, and females in heat must not be transported in the same primary enclosures as males. No more than two live puppies 8 weeks to 6 months old, of comparable size, and weighing 9 kg (20 lb) or less each may be transported by air in the same primary enclosure. Older dogs and puppies weighing more than 9 kg (20 lb) should be individually housed. Weaned littermates that are less than 8 weeks old and are accompanied by their dam may be transported in the same enclosure to research facilities, either by air or surface transport. During transport by surface vehicle, no more than four dogs 8 weeks old or older and of comparable size may be transported in the same primary enclosure.

When viral-antibody-free (unvaccinated) dogs are transported between facilities, precautions must be taken to avoid contact with infectious agents. Some commercial suppliers have developed filtered shipping containers to

transport those dogs. IATA rules require that special measures be taken to ensure that ventilation rates are maintained within the container, that the container be appropriately labeled, that sufficient water be provided for the entire journey, and that food, if required, be provided at the point of origin (IATA, 1993).

Environmental Conditions

At all times, containers holding dogs should be placed in climate-controlled areas that provide protection from the elements (9 CFR 3.13, 3.15, 3.18-3.19). Trucks and planes must be ventilated and provide air that has adequate oxygen and is free of harmful gases and particulate contaminants. Airlines should always place dogs in pressurized compartments. Dogs may be shipped if temperatures will fall below 7.2°C (45°F) during any portion of their journey only if a veterinarian certifies in writing that they have been acclimated to lower temperatures and states the lowest temperature to which they have been acclimated. During transit, dogs must not be exposed to ambient temperatures exceeding 29.4°C (85°F) for a period of more than 4 hours.

Food and Water

All dogs must be offered food and water within 4 hours of delivery to the carrier (9 CFR 3.13c). Carriers must offer water to each dog at 12-hour intervals beginning 12 hours after the shipper last offered water. Adult dogs must be fed at least once every 24 hours, and puppies less than 16 weeks old must be fed every 12 hours throughout the trip. Feeding and watering utensils must be firmly secured to the inside of the container and placed so that they can be filled from outside the container. Written instructions for feeding and watering in transit must be attached to the primary enclosure in such a way that they are easily seen and read (9 CFR 3.16).

Other Requirements

There are special requirements for animal holding areas of terminal facilities, including rules for sanitization, pest control, ventilation, temperature control, and shelter from direct sunlight, rain, snow, and extreme heat (9 CFR 3.18).

Each dog must be accompanied by a health certificate, issued by a licensed veterinarian not more than 10 days before shipping, that states that the dog is free of any infectious disease or physical abnormality that would endanger it or other animals or pose a threat to public health. An exemp-

tion can be made by the secretary of USDA for individual animals shipped to research facilities if the facilities require animals that are not elegible for certification (9 CFR 2.78b). Instructions for the administration of drugs or provision of other special care must be firmly attached to the outside of the container (9 CFR 3.14h). A pregnant bitch should be accompanied by a certificate, signed by a veterinarian, that states that there is no risk of birth during transit (IATA, 1993).

Carriers and intermediate handlers must not accept dogs more than 4 hours before the scheduled departure (6 hours by special arrangement). An attempt must be made to notify the recipient on arrival at the destination and at least once every 6 hours thereafter (9 CFR 3.13f). During shipment by surface transportation, the operator of the conveyance or someone accompanying the operator must observe the dogs at least once every 4 hours to ascertain that they have sufficient air for normal breathing and are not in distress and that the rules for ambient temperature and all other AWR requirements are met. The same rules apply in air carriers if the animal cargo area is accessible during flight. If it is not accessible, the carrier must observe the dogs at loading and unloading. Dogs in physical distress must receive veterinary care as soon as possible (9 CFR 3.17).

REFERENCES

AAFCO (Association of American Feed Control Officials), Canine Nutrition Expert Subcommittee, Pet Food Committee. 1993. AAFCO nutrient profiles for dog foods. Pp. 92-99 in Official Publication 1993. Atlanta: Association of American Feed Control Officials. Available from Charles P. Frank; AAFCO Treasurer; c/o Georgia Department of Agriculture; Plant Food, Feed, and Grain Division; Capitol Square, Atlanta, GA 30334.

Bellhorn, R. W. 1980. Lighting in the animal environment. Lab. Anim. Sci. 30(2): 440-450.

Besch, E. L. 1985. Definition of laboratory animal environmental conditions. Pp. 297-315 in Animal Stress, G. P. Moberg, ed. Bethesda, Md.: American Physiological Society.

Besch, E. L. 1990. Environmental variables and animal needs. Pp. 113-131 in The Experimental Animal in Biomedical Research. Vol. I: A Survey of Scientific and Ethical Issues for Investigators, B. E. Rollin and M. L. Kesel, eds. Boca Raton, Fla.: CRC Press.

Besch, E. L. 1991. Temperature and humidity control. Pp. 154-166 in Handbook of Facilities Planning. Vol. 2: Laboratory Animal Facilities, T. Ruys, ed. New York: Von Nostrand Reinhold.

Besch, E. L. 1992. Animal facility ventilation air quality and quantity. ASHRAE Trans. 98(pt. 2):239-246.

Britz, W. E., Jr. 1990. Caging systems for dogs under the new standards of the Animal Welfare Act. Pp. 48-50 in Canine Research Environment, J. A. Mench and L. Krulisch, eds. Bethesda, Md.: Scientists Center for Animal Welfare. Available from SCAW, 4805 St. Elmo Avenue, Bethesda, MD 20814.

Campbell, S. A., H. C. Hughes, H. E. Griffin, M. S. Landi, and F. M. Mallon. 1988. Some effects of limited exercise on purpose-bred beagles. Am. J. Vet. Res. 49:1,298-1,301.

Clark, J. D., J. P. Calpin, and R. B. Armstrong. 1991. Influence of type of enclosure on exercise fitness of dogs. Am. J. Vet. Res. 52:1,024-1,028.

Clough, G., and M. R. Gamble. 1976. Laboratory Animal Houses. A Guide to the Design and

Planning of Animal Facilities. LAC Manual Series No. 4. Carshalton, Surrey, U.K.: Medical Research Council Laboratory Animals Centre. 44 pp.

Edwards, R. G., M. F. Beeson, and J. M. Dewdney. 1983. Laboratory animal allergy: The measurement of airborne urinary allergens and the effect of different environmental conditions. Lab. Anim. (London) 17:235-239.

Fuller, J. L. 1970. Genetic influences on socialization. Pp. 7-18 in Early Experiences and the Process of Socialization, R. A. Hoppe, G. A. Milton, and E. C. Simmel, eds. New York: Academic Press.

Gorton, R. L., and E. L. Besch. 1974. Air temperature and humidity response to cleaning water loads in laboratory animal storage facilities. ASHRAE Trans. 80(pt. 1):37-52.

Gorton, R. L., J. E. Woods, and E. L. Besch. 1976. System load characteristics and estimation of annual heat loads for laboratory animal facilities. ASHRAE Trans. 82(pt. 1):107-112.

Hetts, S., J. D. Clark, J. P. Calpin, C. E. Arnold, and J. M. Mateo. 1992. Influence of housing conditions on beagle behaviour. Appl. Anim. Behav. Sci. 34:137-155.

Hite, M., H. M. Hanson, N. R. Bohider, P. A. Conti, and P. A. Mattis. 1977. Effect of cage size on patterns of activity and health of beagle dogs. Lab. Anim. Sci. 27:60-64.

Hubrecht, R. C. 1993. A comparison of social and environmental enrichment methods for laboratory housed dogs. Appl. Anim. Behav. Sci. 37:345-361.

Hubrecht, R. C., J. A. Serpell, and T. B. Poole. 1992. Correlates of pen size and housing conditions on the behaviour of kennelled dogs. Appl. Anim. Behav. Sci. 34:365-383.

Hughes, H. C., and S. Campbell. 1990. Effects of primary enclosure size and human contact. Pp. 66-73 in Canine Research Environment, J. A. Mench and L. Krulisch, eds. Bethesda, Md.: Scientists Center for Animal Welfare. Available from SCAW, 4805 St. Elmo Avenue, Bethesda, MD 20814.

Hughes, H. C., S. Campbell, and C. Kenney. 1989. The effects of cage size and pair housing on exercise of beagle dogs. Lab. Anim. Sci. 39:302-305.

IATA (International Air Transport Association). 1993. IATA Live Animal Regulations, 20th ed. Montreal, Quebec: International Air Transport Association. Available from IATA, Publications Department, 2000 Peel Street, Montreal, Quebec, Canada H3A 2R4.

Kealy, R. D., S. E. Olsson, K. L. Monti, D. F. Lawler, D. N. Biery, R. W. Helms, G. Lust, and G. K. Smith. 1992. Effects of limited food consumption on the incidence of hip dysplasia in growing dogs. J. Am. Vet. Med. Assoc. 201:857-863.

Kendall, P. T., and I. H. Burger. 1980. The effect of controlled and appetite feeding on growth and development in dogs. Pp. 60-63 in Proceedings of the Kal Kan Symposium for the Treatment of Dog and Cat Diseases (Sept. 29-30, 1979), R. L. Wyatt, ed. Vernon, Calif.: Kal Kan Foods, Inc. Available from Kal Kan Foods, Inc., 3250 E 44th Street, Vernon, CA 90058-0853.

King, J. A. 1954. Closed social groups among domestic dogs. Proc. Am. Philos. Soc. 98:327-336.

Kirk, R. W., and J. D. Bonagura, eds. 1992. Current Veterinary Therapy. XI. Small Animal Practice. Philadelphia: W. B. Saunders. 1,346 pp.

Lewis, L. D., M. L. Morris, Jr., and M. S. Hand. 1987. Small Animal Clinical Nutrition III. Topeka, Kans.: Mark Morris Associates. Available from Mark Morris Associates, 5500 SW 7th Street, Topeka, KS 66606.

McKelvie, D. H., and F. T. Shultz. 1964. Methods of observing and recording data in long-term studies on beagles. Lab. Anim. Care 14:118-124.

Neamand, J., W. T. Sweeney, A. A. Creamer, and P. A. Conti. 1975. Cage activity in the laboratory beagle: A preliminary study to evaluate a method of comparing cage size to physical activity. Lab. Anim. Sci. 25:180-183.

Newberne, P. M., and J. G. Fox. 1978. Chemicals and toxins in the animal facility. Pp. 118-141 in Laboratory Animal Housing. Proceedings of a symposium organized by the Insti-

tute of Laboratory Animal Resources Committee on Laboratory Animal Housing. Washington, D.C.: National Academy of Sciences.

Newton, W. M. 1972. An evaluation of the effects of various degrees of long-term confinement on adult beagle dogs. Lab. Anim. Sci. 22:860-864.

NRC (National Research Council), Institute of Laboratory Animal Resources, Committee on Care and Use of Laboratory Animals. 1985a. Guide for the Care and Use of Laboratory Animals. NIH Pub. No. 86-23. Washington, D.C.: U.S. Department of Health and Human Services. 83 pp.

NRC (National Research Council), Board on Agriculture, Subcommittee on Dog Nutrition, Committee on Animal Nutrition. 1985b. Nutrient Requirements of Dogs, revised ed. Washington, D.C.: National Academy Press. 79 pp.

Pekrul, D. 1991. Noise control. Pp. 166-173 in Handbook of Facilities Planning. Vol. 2: Laboratory Animal Facilities, T. Ruys, ed. New York: Von Nostrand Reinhold.

Peterson, E. A. 1980. Noise and laboratory animals. Lab. Anim. Sci. 30:422-439.

Poffenbarger, E. M., M. L. Chandler, S. L. Ralston, and P. N. Olson. 1990. Canine neonatology. Part 1. Physiologic differences between puppies and adults. Compend. Cont. Educ. Pract. Vet. 12:1601-1609.

Riley, R. D., and R. K. Blackford. 1991. ALACARTE—An animal in-life tracking system. AALAS Bull. 30(3):20-23. Available from the American Association for Laboratory Animal Science, 70 Timber Creek Drive, Suite 5, Cordova, TN 38018.

Ruckenbusch, Y. 1975. The hypnogram as an index of adaptation of farm animals to changes in their environment. Appl. Anim. Ethol. 2:3-18.

Scott, J. P., and J. L. Fuller. 1965. Genetics and the Social Behavior of the Dog. Chicago: University of Chicago Press. 468 pp.

Sierens, S. E. 1976. The Design, Construction, and Calibration of an Acoustical Reverberation Chamber for Measuring the Sound Power Levels of Laboratory Animals (thesis for M.S. degree). Gainesville: University of Florida. 127 pp. Available from Health Science Center Library, University of Florida, Box 100206, Gainesville, FL 32610-0206.

Stanley, W. C. 1965. The passive person as a reinforcer in isolated beagle puppies. Psychon. Sci. 2:21-22.

Stanley, W. C., and O. Elliot. 1962. Differential human handling as reinforcing events and as treatment influencing later social behavior in basenji puppies. Psychol. Rep. 10:775-788.

Wolfle, T. L. 1990. Policy, program and people: The three P's to well-being. Pp. 41-47 in Canine Research Environment, J. A. Mench and L. Krulisch, eds. Bethesda, Md.: Scientists Center for Animal Welfare. Available from SCAW, 4805 St. Elmo Avenue, Bethesda, MD 20814.

4

Management of Breeding Colonies

REPRODUCTION

To maintain the breeding efficiency of a colony or to breed an important individual dog successfully, staff must understand the unique reproductive characteristics of dogs. The biology of canine reproduction has been extensively reviewed (Burke, 1986; Christiansen, 1984; Concannon, 1991; Concannon and Lein, 1989; Concannon et al., 1989). Information on heritability of physical and other characteristics of dogs, Mendelian genetics of breeding, the incidence and characteristics of diseases that have a genetic basis, and methods for demonstrating heritability is also available (Patterson, 1975; Patterson et al., 1989; Shultz, 1970; Willis, 1989).

Reproductive Cycle of the Bitch

Most bitches can become pregnant once or twice a year. Each ovarian cycle consists of the following phases:

- A follicular phase, or proestrus, during which there is progressive vulval swelling and a serosanguineous (bloody) vaginal discharge. During this period, which can last from 3 days to 3 weeks, the bitch's blood has high concentrations of estrogen. The male will show interest, but he either does not or is not allowed to mount.
- A periovulatory period, or estrus, during which estrogen declines

and progesterone increases as the ovarian corpora lutea form. This period is also the early luteal phase of the cycle. During estrus, which can last from 3 days to 3 weeks, the bitch assumes a characteristic posture in the presence of a male in which the rump is raised and there is a curvature of the back (lordosis) and the tail is held to one side (flagging). The male is allowed to mount, and copulation occurs.

- A midluteal and late luteal phase or metestrus (either pregnant or nonpregnant metestrus), which lasts about 2 months and during which serum progesterone remains elevated above 1 ng/ml.
- A period of weak ovarian activity, or anestrus, lasting 2-10 months, in which progesterone concentration is low, and there is no evidence of estrogen stimulation of the uterus or vulva.

In constant photoperiods of 12 hours of light and 12 hours of darkness or 14 hours of light and 10 hours of darkness, estrous periods should occur with equal incidence throughout the year. Possible effects of constant light have not been studied. With natural circannual changes in photoperiod, bitches come into estrus more frequently in winter and spring months than in summer and autumn months. In most breeds, the interval between estrous periods averages 7-8 months. After the age of 8 years, however, the interval between cycles begins to lengthen, reaching 12 months or longer by the age of 12 years (Andersen and Simpson, 1973).

Successful breeding requires that observation of reproductive conditions be given high priority, and staff must be able to recognize the start of proestrus. A swollen vulva might not be obvious on a dark or long-haired dog, and bitches often lick away the bloody discharge; therefore, the vulva of each breeding bitch must be examined closely two or three times a week, beginning 4 months after estrus.

Vaginal cytology can be useful for estimating the best time for breeding (Concannon and DiGregorio, 1986; Holst, 1986; Olson et al., 1984) and predicting the time of whelping, which will be 55-60 days after a change in the smear indicates late estrus. Vaginal smears in anestrus are nondescript, with a few leukocytes and small epithelial cells. In early proestrus, smears include a high proportion of rounded epithelial cells, erythrocytes, and sometimes a few leukocytes. During midproestrus, there is an increasing percentage of cornified (flakelike) epithelial cells but no leukocytes. All or nearly all epithelial cells in the smear are cornified from 2-8 days before ovulation until 4-9 days after ovulation, when these cells predictably and abruptly decline. In early metestrus, cornified cells are replaced by rounded, smaller superficial cells, and there is usually an influx of leukocytes. The metestrus smear slowly regresses to the nondescript anestrus smear. Smears should be taken from the anterior vagina. They should be obtained and prepared carefully with saline-moistened swabs and should not be contaminated with

vulval material. In the case of bitches that have had reproductive problems, when a successful breeding is important, or both, more accurate predictions can be made by monitoring the progesterone concentration in the serum or plasma with an enzyme-linked immunosorbent assay (ELISA) kit (Bouchard et al., 1991a; Hegstad and Johnston, 1992; Johnston and Romagnoli, 1991). In this test, ovulation occurs a mean of 1-2 days after the initial rise in progesterone, peak fertility a mean of 0-4 days after the initial rise, loss of fertility 6-11 days after, implantation 18-20 days after, and parturition 63-65 days after (Concannon, 1991).

Mating

Theoretically, it is sufficient to maintain one male for every 10-20 females; however, in practice this ratio might not be adequate, for several reasons. First, a bitch in proestrus produces pheromones that will start proestrus in other bitches in the colony, making it likely that several bitches will be in estrus simultaneously. Because mating an individual male more often than once each day can reduce its sperm output after 1 week (Amann, 1986), a greater ratio of males to females might be required to maintain breeding efficiency. Second, except under special circumstances, such as reproducing a disease model, breeding programs should conscientiously avoid inbreeding, and it has been estimated that a ratio greater than two males for each 10 females is needed to prevent an increase in the coefficient of inbreeding (Shultz, 1970).

Natural Mating

Mating can be done naturally or by artificial insemination with fresh or frozen and thawed semen. Provided that the male is healthy, it is not necessary to take special precautions or to use medications to treat the genitalia because the vagina is not a sterile environment. However, it is important to ascertain that neither the dog nor the bitch has canine brucellosis, a disease that seriously affects reproduction and is a zoonosis (see "Control of Infectious Diseases" in Chapter 5). The bitch is usually taken to the stud dog's pen or cage, because a dog will often ignore the bitch or spend an inordinate amount of time scent-marking if he is moved to new surroundings. The bitch should be mated on 2 or 3 days over a 3- to 5-day period. Unless the staff is experienced in distinguishing early proestrus from estrus, the bitch should be presented to the male for 10-15 minutes every day or every other day from the time she is found to be in proestrus until she is mated. Breeding pairs should not be left unattended, because some bitches are highly selective in choosing mates and it is not uncommon for a bitch to attack a dog that is not of her choosing. In addition, the dog might need

assistance until he attains a copulatory lock. Mating should be recorded only on the basis of observations of copulatory locks that last several minutes or more. If a bitch refuses a particular dog, even when signs of estrus (lordosis and flagging) are present, placing her with a different dog might solve the problem. If it is important to the breeding program that a bitch be bred to a dog that she is refusing, a caretaker should restrain her in a manner that will prevent her biting either the caretaker or the stud dog during breeding, or artificial insemination (AI) should be used.

To ensure accuracy of parentage, the same stud must be used for every breeding within a single estrus to avoid multiple-sire litters. Bitches allow dogs to mate from several days before ovulation until several days after ovulation. Because the events of pregnancy are related to the time of ovulation—not necessarily to the time of mating—parturition can occur 56-68 days after a single mating and up to 70 days after the first of multiple matings. Sperm can survive 6 days or more in the bitch, and ovulated eggs can remain fertile for 3-7 days. Parturition should occur 62, 63, or 64 days after ovulation in nearly every bitch (Concannon et al., 1983). Bitches that whelp 56-60 days after the first mating often have small litters, probably because they were bred at the end of the fertile period (P. Concannon, New York State College of Veterinary Medicine, Cornell University, Ithaca, N. Y., unpublished).

Artificial Insemination

AI can be helpful when males cannot be moved easily within or between facilities, when breeding females with weak or selective estrus behavior, when using males that cannot provide natural service, and for preserving valuable animal models. Semen collection, handling of semen, and insemination are described in detail elsewhere (Christiansen, 1984; Concannon and Battista, 1989).

Insemination with fresh semen. Semen can be collected in a clean paper cup or in a latex cone (artificial vagina) attached to a 15-ml conical polypropylene centrifuge tube. An advantage of the former method is that debris from the penis is less likely to become mixed in the ejaculate. Ejaculate should be maintained at room or skin temperature and should be checked microscopically for sperm viability and malformations. Any variation from the expected chalky white color or 1- to 5-cc volume should be recorded. The full ejaculate should be deposited into the anterior vagina with a clean plastic pipet attached to a syringe with nonrubber (e.g., polypropylene) tubing. The hindquarters of the bitch should be raised for 10 minutes while the vagina is manipulated digitally by an attendant wearing a clean glove. The bitch should not be allowed to sit for 20 minutes, and pressure on her

abdomen should be avoided. AI should be performed every other day until two or three inseminations have been accomplished. The precise timing for performing AI can be predicted by checking for softening of the vulva, which often occurs around the time of ovulation; by demonstrating the appropriate vaginal cytologic characteristics of advanced estrus; or by measuring the initial rise in serum or plasma progesterone. Ideally, two inseminations should occur before vaginal smears show reduced cornification.

Insemination with fresh chilled semen. Fresh semen can be diluted or extended in one of several laboratory buffers or commercial extenders and shipped refrigerated by overnight express for use in insemination in another location (Concannon and Battista, 1989). At 4°C (39.2°F), sperm motility remains nearly normal for 3-4 days if the semen is diluted in an appropriate diluent and for 1 day if undiluted (see Morton and Bruce, 1989).

Insemination with frozen semen. Frozen semen should be thawed and handled according to the instructions provided by the laboratory that processed it, because each freezing technique has stringent requirements for rate of thawing, dilution, and site of deposition. Although sperm live for several days in fresh semen, they normally die within a few hours after thawing; therefore, precise timing of insemination is important for successful impregnation. The best time to inseminate is usually shortly after oocyte maturation, which occurs 5-6 days after the initial rise in progesterone, around the time of a surge in leutinizing hormone. In most bitches, the inseminations should also take place 2-4 days before the decrease in vaginal cornification. Reported success rates for vaginal insemination range from 0 to 70 percent (Concannon and Battista, 1989); success probably depends heavily on the freezing method and the number of viable sperm inseminated. Success rates of 50-90 percent have been reported for uterine insemination, which is accomplished surgically or with special instrumentation to deposit sperm through the cervix (Concannon and Battista, 1989).

Pregnancy and Parturition

Pregnancy can be determined at 25 days after ovulation by ultrasonography, at 20-35 days after ovulation with palpation, and at 45 days after ovulation with radiography (Johnson, 1986; Yeager and Concannon, 1990). There are no well-documented biochemical or immunologic canine pregnancy tests available. Concannon (1991) has reviewed changes in body weight during pregnancy and pregnancy-specific changes in hematocrit, serum chemistry, and metabolism.

Whelping facilities should provide seclusion from excessive noise and other disturbances. The whelping box should be large enough to accommo-

date the bitch and pups and have sides high enough to prevent neonates from wandering out of the box. The bottom of a large, fiberglass shipping crate works well for beagle-size dogs. The whelping box should be provided about a week before expected parturition.

Johnson (1986) has reviewed the management of the pregnant bitch. A nonpurulent green discharge, anorexia, and restlessness are normal just before parturition. Birth of a litter can be either rapid or protracted over much of a day. Intervals between pups normally range from 20 minutes to 3 hours. Intervals greater than 3 hours can indicate a problem with fetal position or uterine function and warrant veterinary attention. Persistent, unproductive labor of more than 1 hour also requires veterinary attention (Johnston and Romagnoli, 1991; Jones and Joshua, 1988).

NEONATAL CARE

Newborn pups, like all neonatal mammals, have poorly developed temperature-control mechanisms; therefore, it is necessary to keep the temperature in the whelping box higher than room temperature. Temperatures of 29.4-32.2°C (85-90°F) have been suggested for the first 7 days of life, 26.7°C (80°F) for days 8-28, 21.1-23.9°C (70-75°F) for days 29-35, and 23.9°C (70°F) thereafter (Poffenbarger et al., 1990). That can be done by raising the temperature of the room and placing insulation between the whelping box and the cage or floor or by using heating devices, such as heat lamps or built-in heating elements. However, caution is necessary in using such heating devices; because pups younger than 7 days old have very slow withdrawal reflexes (Breazile, 1978), they can be overheated or severely burned by these devices. Circulating-water heating pads or commercial pig warmers are useful, because they maintain heat at a safe level.

Whelping boxes should be examined two or more times a day for evidence of maternal neglect or cannibalism and for problems with the pups. A normal pup is plump and round, its head is mobile, and it exhibits a rooting reflex. Breathing is regular and unlabored, and the coat is shiny and free of debris. Abdominal enlargement after nursing is normal, but abdominal enlargement accompanied by restlessness, weakness, and either excessive vocalization or complete silence can indicate illness or aerophagia. Failure to gain weight is often the first sign of illness in a newborn animal (Greco and Watters, 1990). Andersen (1970) reported expected weight gains for beagle pups.

Dead pups should be removed from the box. Andersen (1970) and Lawler (1989) have reviewed causes of neonatal deaths and have reported an average rate of death of about 20 percent. Necropsy examination is suggested for all pups that die or are euthanatized with severe illness. Such examinations are necessary to distinguish between congenital defects, which affect only the pups in which they occur; infectious diseases, whose spread

might be prevented; and problems with the dam (e.g., insufficient milk) or the environment (e.g., room temperature too low), which can be corrected.

REPRODUCTIVE PROBLEMS

False Estrus and Anestrus

Recurrent frequent false estrus (estrus without ovulation) has been reported (Shille et al., 1984). In false estrus, estrus appears normal, and bitches will mate but fail to conceive. False estrus can be confirmed by demonstrating with a progesterone ELISA kit that the serum or plasma progesterone concentration has not risen above 1 ng/ml, as would be expected for 50 days or more after ovulation if estrus were normal. Bitches that often have false estrus or have false estrus followed in a few weeks by normal estrus cause problems in maintaining breeding colonies. Except in special circumstances, such as reproducing a disease model, it is preferable to cull these animals. Culling based on small litter size, problems with whelping or maternal behavior, chronic infertility, or persistent anestrus is also appropriate. Methods for assessment and treatment for potential causes of infertility in females have been extensively reviewed (Feldman and Nelson, 1987; Johnston and Romagnoli, 1991; Shille, 1986). Persistent anestrus can be distinguished from unobserved cycles only through extremely careful examinations for signs of proestrus or progesterone assays every 6 weeks. Estradiol assays are not particularly informative, and assays of canine gonadotropin to diagnose primary gonadal failure are not readily available. Attempts to induce estrus in anestrus bitches have had variable success (Bouchard et al., 1991b; Concannon, 1992; Concannon et al., 1989).

Delayed Parturition

Whelping should not be considered overdue until 67 days after the last mating or possibly 70 or more days after the first of several matings. Cesarean section should not be contemplated earlier unless there are obvious signs of distress in the bitch. Johnson (1986) and Jones and Joshua (1988) have reviewed veterinary management of dystocia.

Pseudopregnancy

Bitches that are not bred or that are bred but fail to become pregnant frequently exhibit pseudopregnancy because of the progesterone secretion that always follows ovulation. Signs of pseudopregnancy include extensive mammary development, lactation, and maternal behavior. Pseudopregnancy is rare in beagles but more common in other breeds. It is self-limiting and usually does not require intervention (Feldman and Nelson, 1987).

SPECIAL NUTRITIONAL REQUIREMENTS

Bitches

During pregnancy and lactation, bitches should be fed a diet approved by the Association of American Feed Control Officials for all life stages or a diet specially formulated for gestation and lactation (see "Selecting Optimal Rations" in Chapter 3). When a quality diet is fed, supplementation with vitamins and minerals is neither necessary nor desirable.

During the first two-thirds of pregnancy, the amount fed should be the same as that fed before pregnancy. During the last trimester, food intake should be gradually increased so that at parturition it is 150 percent of the daily maintenance requirement. Bitches should not be permitted to become obese during gestation, because this condition can increase the risk of dystocia and postparturient metabolic disorders (Johnston, 1986). Bitches that are underfed during gestation tend to have a higher incidence of stillbirths than bitches that are fed appropriate amounts, and their pups often weigh less at birth (Holme, 1982).

Lactation represents the greatest nutrient challenge that bitches experience during their lifetimes. For the first 3 weeks after parturition, nutrient requirements increase rapidly, leveling off at 200-250 percent of daily maintenance requirements, or even more, depending on the number of nursing pups (NRC, 1985). The nutritional demands of lactation are met best through free access to both food and water. At the time of weaning, food is generally withheld for 24 hours to decrease milk production. Food intake for the first day after weaning should be one-fourth of the amount required for maintenance and then gradually increased to the maintenance requirement by day 4. Ideally, lactating bitches should be within 15 percent of their prebreeding body weight at the time of weaning (AAFCO, 1993).

Pups

Pups should be maintained exclusively on their dams' milk until they are 3 weeks old. They can then begin to eat small amounts of a moistened gestation-lactation diet or a growth diet. Most pups can be weaned completely onto this type of diet by the age of 6-8 weeks. For the development of normal social behavior, it is desirable that they not be completely weaned before they are 6 weeks old. Pups that cannot be nursed by their dam or a foster dam before they are 5 weeks old should be fed one of the commercially available, complete milk replacers. Pups can be fed with bottles and nipples or stomach tubes. Bottles and nipples should be thoroughly cleaned after each use. If a stomach tube is used, its proper placement can be

ensured by inserting it to a distance equal to the premeasured distance from the mouth to the last rib. A small amount of sterile saline solution should be introduced through the tube before milk replacer is injected. After each meal, orphaned pups should be massaged in the anal-genital region with a warm, wet cotton ball to stimulate urination and defecation. Most orphans can be completely weaned onto solid food by 5 weeks of age.

Young pups most readily eat canned or moistened dry food; older pups can be fed dry, semi-moist, or canned food. Pups can be fed on either a free-choice or meal-feeding program. If a meal-feeding program is used, they should be fed at least four times a day until they are 3 months old, three times a day until they reach two-thirds of their adult weight, and two times a day thereafter. After the age of 3 months, free-choice programs can lead to obesity in small breeds and faster than optimal growth in large breeds. Excessively rapid growth in breeds whose weight at maturity is more than 30 lb has been associated with an increase in the incidence of several metabolic bone diseases (Hedhammer, 1981; Hedhammer et al., 1974; Kealy et al., 1992). Pups should be fed so that they grow at near optimal rates; growth-curve data are often available from pet-food manufacturers. When an appropriate growth ration is fed, no supplementation is necessary. If a product is not capable of supporting an optimal growth rate, it is generally safer, less expensive, and more convenient to switch to a better-quality growth diet. As a general rule, pups gain approximately 1-2 g/day per pound of anticipated adult body weight (Lewis et al., 1987). An inappropriate growth rate usually reflects a problem with the ration being fed or with the pups' access to it.

VACCINATION AND DEWORMING

Annual vaccinations and deworming of brood bitches should be scheduled for anestrus or weaning periods, not when bitches are in proestrus or are pregnant.

Pups that have nursed on colostrum during the first 12 hours after birth have received passive immunity to viruses against which the dam was immunized. If pups cannot nurse on colostrum, 16 ml of pooled serum administered subcutaneously has been shown to be a successful alternative (Bouchard et al., 1992). Maternally acquired immunity declines over time, and the rate of decline, although variable, depends on the level of the dam's immunity at parturition and the amount of colostrum ingested by each pup. About 30-50 percent of pups will be susceptible to disease and capable of being effectively vaccinated by the age of 6-7 weeks. Most pups (more than 95 percent) can be effectively vaccinated by the age of 16 weeks. General principles of immunity in newborn animals and of immunoprophylaxis are reviewed elsewhere (Carmichael, 1983; Tizard, 1977a,b). Diseases to which pups are

susceptible and vaccination schedules are discussed in Chapter 5, Veterinary Care.

Roundworms (*Toxocara canis*) and hookworms (*Ancylostoma caninum* and *A. braziliense*) are endoparasites that commonly infect young pups. Roundworms are typically transmitted from bitches to pups in utero, and pups begin to shed eggs in their feces 3 weeks after birth. Pups infected with hookworm larvae in their dams' milk typically begin to pass eggs in their feces 2 weeks after birth. It is important that pups receive treatment early in life if infection with roundworms or hookworms is suspected. To prevent peracute hookworm disease in unweaned pups of bitches harboring large numbers of somatic larvae, it might be necessary to treat the pups before hookworm eggs are detectable in fecal examinations. Canine endoparasites are reviewed in Chapter 5 and discussed fully elsewhere (Georgi and Georgi, 1992).

SOCIALIZATION OF PUPS

There is ample evidence of the importance of adequate socialization for the normal behavioral development of dogs (Clarke et al., 1951; Fox, 1968; Freedman et al., 1961; Houpt, 1991; Scott and Fuller, 1965). The term *socialization* is somewhat confusing because it has been used to describe events, processes, and procedures. In the narrowest sense, socialization is the development of the primary social attachments that form between a pup, its dam, and its littermates during a critical or sensitive period in its behavioral development (Scott, 1968). The process is not peculiar to dogs but occurs in many species of social mammals (see, for example, Cairns, 1966; Harlow and Harlow, 1969). In a broader sense, socialization is the process by which pups form attachments to other dogs, people, and environments. Attachment formation might require nothing more than sufficient exposure to or experience with other dogs, people, and elements of the environment, which results in familiarity with a variety of stimuli (Cairns, 1966; Scott, 1963). Breeds and individual pups differ in ease of socialization (Scott, 1970). In any case, adequate socialization allows a pup to develop normal social relationships with other dogs and to adapt to pair or group housing, to adjust more easily to unfamiliar stimuli and environmental changes, and to accept handling with little or no fear and distress (Scott, 1980).

Sensitive Period for Socialization

There is a sensitive period for socialization during which attachments form most readily and rapidly (Scott and Fuller, 1965). The beginning of the period is marked by the startle response to sound at the age of approximately 3 weeks. Also at 3 weeks, a pup begins to display distress vocaliza-

tions when separated from its dam. Distress vocalizations are distinct from those made in response to fear (Davis et al., 1977), hunger (Compton and Scott, 1971; Scott and Bronson, 1964), or physical discomfort (Gurski et al., 1980). Separation distress is greater in an unfamiliar pen (Elliot and Scott, 1961). To minimize separation distress, pups should remain with their dams for at least their first 6 weeks.

Ease of attachment formation varies between breeds and individuals but generally peaks between the age of 6-8 weeks (Scott and Bronson, 1964). Although socialization probably occurs at a low rate throughout life, the end of the sensitive period is marked by the pup's increasing fear of the unfamiliar at the age of 12-14 weeks (Scott, 1962).

Consequences of Inadequate Socialization

Pups that are inadequately socialized during the sensitive period exhibit abnormal behaviors, called kennel-dog or isolation syndromes, that are characterized by one or more of the following behaviors: generalized fearfulness, fear-motivated aggression, timidity, immobility, or hyperactivity (Scott et al., 1967). Dogs that, as a result of inadequate socialization, become highly distressed when subjected to common laboratory procedures (e.g., handling, walking on a leash, restraint, venipuncture, moves to different enclosures, and contact with other dogs) probably do not make good research subjects and might be in a compromised state of well-being. It has been reported that physiologic measurements on such dogs can fall outside normal limits (Vanderlip et al., 1985b).

Socialization Programs

Providing contact and handling only during routine husbandry procedures might not be sufficient to produce behaviorally normal, cooperative research animals (Vanderlip et al., 1985a,b). Specific programs that address each aspect of socialization—to dogs, to people, and to the environment—should be implemented. Programs that can be used as examples for providing adequate socialization have been reported (Vanderlip et al., 1985a,b; Wolfle, 1990).

The following are examples of elements that might be included in socialization programs: positive contacts with more than one person, opportunities to follow handlers, introduction to some type of restraint (e.g., a collar and leash), contacts with conspecifics other than littermates, and opportunities to explore outside the kennel. Exploration might include exposure to floors of different textures, to a room with different lighting, to stairs, and to such equipment as exam tables, clippers, and scales. Exposures to those elements should be gradual and paired with positive reinforc-

ers, such as food, petting, or verbal praise. Negative reinforcement and physical punishment can elicit aggressive or fearful behaviors and will make pups more difficult to handle. It is not necessary, or practical, to introduce pups to every type of environment, person, or animal to which they will later be exposed in order to provide adequate socialization. Evidence suggests that experience in coping successfully with change facilitates later success (Scott, 1980). Thus, the adequacy of any socialization program can be determined by the ability of pups to adapt successfully to environmental changes with minimal behavioral and physiologic disruption.

RECORD KEEPING

Records on colony reproduction are essential. Individual records should contain the following minimal information on each bitch:

- start date of each proestrus;
- dates of mating and stud dog's identification number;
- date on which bitch's diet should be increased (day 42 of gestation), date to move bitch to whelping facility (day 50), and range of expected whelping dates;
- actual whelping date, whelping complications, number and sex of live pups, number of stillbirths, and any obvious abnormalities in the pups;
- date to start weaning, bitch's distemper antibody titer (if known), and dates to deworm and vaccinate litter; and
- date(s) and details of disposition of litter.

In addition, missed cycles, abortions, or any abnormal maternal behavior should be recorded.

To facilitate review of the reproduction records of an entire colony, it is helpful to have a separate computerized or manual-entry spreadsheet that displays every reproductive cycle of each bitch in the colony. The spreadsheet is most useful if it lists the following information, organized chronologically by date of proestrus:

- identification number of each bitch whose proestrus was first observed on that date;
- for each bitch bred, identification number of stud dog, first and last dates of mating, total number of matings, and calculated or expected dates for medical examinations, moving to whelping facility, and whelping; and
- expected date of next cycle.

The spreadsheet should be updated periodically to include for each bitch the actual whelping date; the length of gestation; litter information, as described

above; the actual date of the next cycle; and the calculated interestrus interval. A computerized list can be sorted to review the breeding records of individual bitches and males over several years. Such a list also allows examination for trends in low fertility, long or short gestation lengths as indicators of poorly timed inseminations, number of matings per cycle, projected periods during which several bitches will be in heat at the same time or no bitches will be in heat, and other matters that could reflect husbandry, management, or staff problems that need correction.

REFERENCES

AAFCO (Association of American Feed Control Officials), Canine Nutrition Expert Subcommittee, Pet Food Committee. 1993. AAFCO nutrient profiles for dog foods. Pp. 92-99 in Official Publication 1993. Atlanta: Association of American Feed Control Officials. Available from Charles P. Frank; AAFCO Treasurer; c/o Georgia Department of Agriculture; Plant Food, Feed, and Grain Division; Capitol Square, Atlanta, GA 30334.

Amann, R. 1986. Reproductive physiology and endocrinology of the dog. Pp. 532-538 in Current Therapy in Theriogenology 2. Diagnosis, Treatment and Prevention of Reproductive Diseases in Small and Large Animals, D. A. Morrow, ed. Philadelphia: W. B. Saunders.

Andersen, A. C. 1970. Reproduction. Pp. 31-39 in The Beagle as an Experimental Dog. Ames: Iowa State University Press.

Andersen, A. C., and M. E. Simpson. 1973. The Ovary and Reproductive Cycle of the Dog (Beagle). Los Altos, Calif.: Geron-X. 290 pp.

Bouchard, G. F., N. Solorzano, P. W. Concannon, R. S. Youngquist, and C. J. Bierschwal. 1991a. Determination of ovulation time in bitches based on teasing, vaginal cytology, and ELISA for progesterone. Theriogenology 35:603-611.

Bouchard, G., R. S. Youngquist, B. Clark, P. W. Concannon, and W. F. Braun. 1991b. Estrus induction in the bitch using a combination diethylstilbestrol and FSH-P. Theriogenology 36:51-65.

Bouchard, G., H. Plata-Madrid, R. S. Youngquist, G. M. Buening, V. K. Ganjam, G. F. Krause, G. K. Allen, and A. L. Paine. 1992. Absorption of an alternate source of immunoglobulin in pups. Am. J. Vet. Res. 53:230-233.

Breazile, J. E. 1978. Neurologic and behavioral development in the puppy. Vet. Clin. North Am. 8:31-45.

Burke, T. J., ed. 1986. Small Animal Reproduction and Infertility. Philadelphia: Lea & Febiger. 408 pp.

Cairns, R. B. 1966. Attachment behavior in mammals. Psychol. Rev. 73:409-429.

Carmichael, L. E. 1983. Immunization strategies in puppies—Why failures? Compend. Contin. Educ. Pract. Vet. 5:1043-1051.

Christiansen, I. J. 1984. Reproduction in the Dog and Cat. London: Balliere Tindall. 309 pp.

Clarke, R. S., W. Heron, M. L. Fetherstonhaugh, D. G. Forgays, and D. O. Hebb. 1951. Individual differences in dogs: Preliminary report on the effects of early experience. Can. J. Psychol. 5:150-156.

Compton, J. M., and J. P. Scott. 1971. Allelomimetic behavior system: Distress vocalization and social facilitation of feeding in Telomian dogs. J. Psychol. 78:165-179.

Concannon, P. W. 1991. Reproduction in the dog and cat. Pp. 517-554 in Reproduction in Domestic Animals, 4th ed., P. T. Cupps, ed. New York: Academic Press.

Concannon, P. W. 1992. Methods for rapid induction of fertile estrus in dogs. Pp. 960-963 in Current Veterinary Therapy. XI. Small Animal Practice, R. W. Kirk and J. D. Bonagura, eds. Philadelphia: W. B. Saunders.

Concannon, P. W., and M. Battista. 1989. Canine semen freezing and artificial insemination. Pp. 1247-1259 in Current Veterinary Therapy. X. Small Animal Practice, R. W. Kirk, ed. Philadelphia: W. B. Saunders.

Concannon, P. W., and G. B. DiGregorio. 1986. Canine vaginal cytology. Pp. 96-111 in Small Animal Reproduction and Infertility, T. Burke, ed. Philadelphia: Lea & Febiger.

Concannon, P. W., and D. H. Lein. 1989. Hormonal and clinical correlates of ovarian cycles, ovulation, pseudopregnancy, and pregnancy in dogs. Pp. 1269-1282 in Current Veterinary Therapy. X. Small Animal Practice, R. W. Kirk, ed. Philadelphia: W. B. Saunders.

Concannon, P., S. Whaley, D. Lein, and R. Wissler. 1983. Canine gestation length: Variation related to time of mating and fertile life of sperm. Am. J. Vet. Res. 44: 1819-1821.

Concannon, P. W., D. B. Morton, and B. J. Weir, eds. 1989. Dog and cat reproduction, contraception and artificial insemination. J. Reprod. Fert. Suppl. 39:1-350.

Davis, K. L., J. C. Gurski, and J. P. Scott. 1977. Interaction of separation distress with fear in infant dogs. Dev. Psychobiol. 10:203-212.

Elliot, O., and J. P. Scott. 1961. The development of emotional distress reactions to separation, in puppies. J. Genet. Psychol. 99:3-22.

Feldman, E. C., and R. W. Nelson. 1987. Canine and Feline Endocrinology and Reproduction. Philadelphia: W. B. Saunders. 564 pp.

Fox, M. W. 1968. Socialization, environmental factors, and abnormal behavioral development in animals. Pp. 332-355 in Abnormal Behavior in Animals, M. W. Fox, ed. Philadelphia: W. B. Saunders.

Freedman, D. G., J. A. King, and O. Elliot. 1961. Critical period in the social development of dogs. Science 133:1016-1017.

Georgi, J. R., and M. E. Georgi. 1992. Canine Clinical Parasitology. Philadelphia: Lea & Febiger. 227 pp.

Greco, D. S., and J. W. Watters. 1990. The physical examination and radiography. Pp. 1-17 in Veterinary Pediatrics: Dogs and Cats from Birth to Six Months, J. D. Hoskins, ed. Philadelphia: W. B. Saunders.

Gurski, J. C., K. Davis, and J. P. Scott. 1980. Interaction of separation discomfort with contact comfort and discomfort in the dog. Dev. Psychobiol. 13:463-467.

Harlow, H. F., and M. K. Harlow. 1969. Effect of various mother-infant relationships on rhesus monkey behaviors. Pp. 34-60 in Determinants of Infant Behavior IV, B. M. Foss, ed. London: Methuen.

Hedhammer, Å. 1981. Nutrition as it relates to skeletal diseases. Pp. 41-44 in Proceedings of the Kal Kan Symposium for the Treatment of Small Animal Diseases (Oct. 11-12, 1980), L. D. Howell, ed. Vernon, Calif.: Kal Kan Foods, Inc. Available from Kal Kan Foods, Inc., 3250 E 44th Street, Vernon, CA 90058-0853.

Hedhammer, Å., F. M. Wu, L. Krook, H. F. Schryver, A. Delahunta, J. P. Whalen, F. A. Kallfelz, E. A. Numez, H. F. Hintz, B. E. Sheffy, and G. D. Ryan. 1974. Overnutrition and skeletal disease. An experimental study in growing Great Dane dogs. Cornell Vet. 64(suppl. 5):1-159.

Hegstad, R. L., and S. D. Johnston. 1992. Use of serum progesterone ELISA tests in canine breeding management. Pp. 943-947 in Current Veterinary Therapy. XI. Small Animal Practice, R. W. Kirk and J. D. Bonagura, eds. Philadelphia: W. B. Saunders.

Holme, D. W. 1982. Practical use of prepared foods for dogs and cats. Pp. 47-59 in Dog and Cat Nutrition, A. T. B. Edney, ed. New York: Pergamon Press.

Holst, P. A. 1986. Vaginal cytology in the bitch. Pp. 457-462 in Current Therapy in Theriogenology 2. Diagnosis, Treatment and Prevention of Reproductive Diseases in Small and Large Animals, D. A. Morrow, ed. Philadelphia: W. B. Saunders.

Houpt, K. A. 1991. Domestic Animal Behavior for Veterinarians and Animal Scientists, 2d ed. Ames: Iowa University Press. 408 pp.

Johnson, C. A., ed. 1986. Reproduction and periparturient care. Vet. Clin. N. Am. 16(3):1-605.

Johnston, S. D. 1986. Parturition and dystocia in the bitch. Pp. 500-501 in Current Therapy in Theriogenology 2. Diagnosis, Treatment and Prevention of Reproductive Diseases in Small and Large Animals, D. A. Morrow, ed. Philadelphia: W. B. Saunders.

Johnston, S. D., and S. E. Romagnoli, eds. 1991. Canine Reproduction. Vet. Clin. N. Am. 21(3):421-640.

Jones, D. E., and J. O. Joshua. 1988. Reproductive Clinical Problems in the Dog, 2d ed. London: Wright. 238 pp.

Kealy, R. D., S. E. Olsson, K. L. Monti, D. F. Lawler, D. N. Biery, R. W. Helms, G. Lust, and G. K. Smith. 1992. Effects of limited food consumption on the incidence of hip dysplasia in growing dogs. J. Am. Vet. Med. Assoc. 201:857-863.

Lawler, D. F. 1989. Care and diseases of neonatal puppies and kittens. Pp. 1325-1333 in Current Veterinary Therapy. X. Small Animal Practice, R. W. Kirk, ed. Philadelphia: W. B. Saunders.

Lewis, L. D., M. L. Morris, Jr., and M. S. Hand. 1987. Dogs—Feeding and Care Pp. 3.1-3.32 in Small Animal Clinical Nutrition III. Topeka, Kans.: Mark Morris Associates. Available from Mark Morris Associates, 5500 SW 7th Street, Topeka, KS 66606.

Morton, D. B., and S. G. Bruce. 1989. Semen evaluation, cryopreservation and factors relevant to the use of frozen semen in dogs. J. Reprod. Fert. Suppl. 39:311-316.

NRC (National Research Council), Board on Agriculture, Subcommittee on Dog Nutrition, Committee on Animal Nutrition. 1985. Nutrient requirements and signs of deficiency. Pp. 2-38 in Nutrient Requirements of Dogs, revised ed. Washington, D.C.: National Academy Press.

Olson, P. N., M. A. Thrall, P. M. Wykes, P. W. Husted, T. M. Nett, and H. R. Sawyer, Jr. 1984. Vaginal cytology. I. A useful tool for staging the canine estrous cycle. Compend. Contin. Educ. Pract. Vet. 6:288-298.

Patterson, D. F. 1975. Diseases due to single mutant genes. J. Am. Anim. Hosp. Assoc. 11:327-341.

Patterson, D. F., G. A. Aguirre, J. C. Fyfe, U. Giger, P. L. Green, M. E. Haskins, P. F. Jezyk, and V. N. Meyers-Wallen. 1989. Is this a genetic disease? J. Small Anim. Pract. 30:127-139.

Poffenbarger, E. M., M. L. Chandler, S. L. Ralston, and P. N. Olson. 1990. Canine neonatology. Part 1. Physiologic differences between puppies and adults. Compend. Cont. Educ. Pract. Vet. 12:1601-1609.

Scott, J. P. 1962. Critical periods in behavioral development. Science 138:949-958.

Scott, J. P. 1963. The process of primary socialization in canine and human infants. Soc. Res. Child Dev. Monogr. 28(1):1-47.

Scott, J. P. 1968. The process of primary socialization in the dog. Pp. 412-439 in Early Experience and Behavior, G. Newton and S. Levine, eds. Springfield, Ill.: Charles C Thomas.

Scott, J. P. 1970. Critical periods for the development of social behaviour in dogs. Pp. 21-32 in The Post-Natal Development of Phenotype, S. Kazda and V. H. Denenberg, eds. Prague: Academia.

Scott, J. P. 1980. The domestic dog: A case of multiple identities. Pp. 129-143 in Species Identity and Attachment: A Phylogenetic Evaluation, M. A. Roy, ed. New York: Garland STPM.

Scott, J. P., and F. H. Bronson. 1964. Experimental exploration of the et-epimeletic or care-soliciting behavioral system. Pp. 174-193 in Psychobiological Approaches to Social

Behavior, P. H. Leiderman and D. Shapiro, eds. Stanford, Calif.: Stanford University Press.

Scott, J. P., and J. L. Fuller. 1965. Genetics and the Social Behavior of the Dog. Chicago: University of Chicago Press. 468 pp.

Scott, J. P., J. H. Shepard, and J. Werboff. 1967. Inhibitory training of dogs: Effects of age at training in basenjiis and Shetland sheepdogs. J. Psychol. 66:237-252.

Shille, V. M. 1986. Management of reproductive disorders in the bitch and queen. Pp. 1225-1229 in Current Veteterinary Therapapy. IX. Small Animal Practice, R. W. Kirk, ed. Philadelphia: W. B. Saunders.

Shille, V. M., M. B. Calderwood-Mays, and M.-J. Thatcher. 1984. Infertility in a bitch associated with short interestrous intervals and cystic follicles: A case report. J. Am. Anim. Hosp. Assoc. 20:171-176.

Shultz, F. T. 1970. Genetics. Pp. 489-509 in The Beagle as an Experimental Dog, A. C. Andersen, ed. Ames: Iowa State University Press.

Tizard, I. R. 1977a. Immunity in the fetus and newborn animal. Pp. 155-168 in An Introduction to Veterinary Immunology. Philadelphia: W. B. Saunders.

Tizard, I. R. 1977b. Immunoprophylaxis: General principles of vaccination and vaccines. Pp. 169-183 in An Introduction to Veterinary Immunology. Philadelphia: W. B. Saunders.

Vanderlip, S. L., J. E. Vanderlip, and S. Myles. 1985a. A socializing program for laboratory-raised canines. Lab Anim. 14(1):33-36.

Vanderlip, S. L., J. E. Vanderlip, and S. Myles. 1985b. A socializing program for laboratory-raised canines. Part 2: The puppy socialization schedule. Lab Anim. 14(2):27-36.

Willis, M. B. 1989. Genetics of the Dog. London: H. F. & G. Witherby. 417 pp.

Wolfle, T. L. 1990. Policy, program, and people: The three P's to well-being. Pp. 41-47 in Canine Research Environment, J. A. Mench and L. Krulisch, eds. Bethesda, Md.: Scientists Center for Animal Welfare. Available from SCAW, 4805 St. Elmo Avenue, Bethesda, MD 20814.

Yeager, A. E., and P. W. Concannon. 1990. Association between the preovulatory luteinizing hormone surge and the early ultrasonographic detection of pregnancy and fetal heartbeats in beagle dogs. Theriogenology 34:655-665.

5

Veterinary Care

Veterinary care in laboratory animal facilities goes beyond the prevention, diagnosis, treatment, and control of disease. It also includes monitoring animal care and welfare and providing guidance to investigators on handling and immobilizing animals and preventing or reducing their pain and distress (NRC, 1985, 1992). Responsibilities of the attending veterinarian are specified by the Animal Welfare Regulations (9 CFR 2.33, research facilities; 9 CFR 2.40, dealers and exhibitors).

The first sections of this chapter deal with the procurement and conditioning of research dogs and the control of infectious and parasitic diseases. Aspects of veterinary care dealing with the use of anesthetics and analgesics, surgery and postsurgical care, and euthanasia are taken up in the last three sections. The medical aspects of reproductive disorders are discussed in Chapter 4; special care for pups is also reviewed in Chapter 4 and addressed in detail elsewhere (Hoskins, 1990). Reference values for blood analytes can be found in textbooks by Kaneko (1989) and Loeb and Quimby (1989).

Dogs can be afflicted with many uncommonly occurring but scientifically interesting diseases and disorders, many of which also afflict humans. Some breeds have predispositions to particular diseases and disorders (e.g., dalmatians are prone to urate bladder stones); a comprehensive review of this subject is available (Willis, 1989). Chapter 6 of this book addresses the maintenance of dogs with selected genetic disorders.

PROCUREMENT

General Considerations

Dogs acquired from outside a research facility's breeding program must be obtained lawfully from dealers licensed by the U.S. Department of Agriculture (USDA) or sources that the USDA has exempted from licensing (7 USC 2137). A *List of Licensed Dealers* can be obtained from Regulatory Enforcement and Animal Care, Animal and Plant Health Inspection Service, USDA, Federal Building, Room 268, 6505 Belcrest Road, Hyattsville, MD 20782. Examples of exempt sources are municipal pounds and people who provide dogs without compensation.

Procurement of dogs for research requires planning by a knowledgeable person to ensure that the dogs receive good care and that the needs of the investigator are met. The person should be familiar with federal regulations applicable to the acquisition of dogs (9 CFR, parts 2 and 3) and with state and local ordinances applicable to the aquisition of dogs from pounds and shelters. It is strongly recommended that institutions inspect vendors' premises for compliance with procurement specifications agreed on by contract before the first dogs are purchased and periodically thereafter.

Sources

Both random-source and purpose-bred dogs can be purchased for research purposes. Random-source dogs are those raised under unknown conditions of breeding and health. Sometimes they are stabilized and conditioned (see below) by the dealer before sale. Purpose-bred dogs are those from known matings that have limited exposure to infectious diseases.

Random-source dogs that have not been stabilized and conditioned by the vendor (often called nonconditioned random-source dogs) are usually acquired from USDA-licensed dealers or, less commonly, from pounds. If a number of dogs of similar weight or body conformation are needed, the purchaser must allow sufficient time for the group to be assembled by the vendor. Random-source dogs that have been stabilized and conditioned (often called conditioned random-source dogs) should be purchased only from vendors that have written standard procedures for their conditioning programs. Purpose-bred dogs are acquired from USDA-licensed dealers that breed dogs specifically for research or from an institutional breeding program. Dogs with diseases of research interest are often acquired from exempt sources, such as pet owners referred by clinical veterinarians.

Conditioning

Conditioning is defined as physiologic and behavioral adjustment to a new environment. The period required for that adjustment to occur is called the conditioning period. Conditioning consists of adjustment to a new regimen, including new people, diet, climate, and exercise. The adjustment can be hastened if the using institution provides the same type of food as the dealer or vendor and uses the same type of automatic watering devices. Physiologic status, as well as the presence of diseases, can be determined by assessing red-cell counts, packed-cell volumes, and white-cell differential counts and by using blood urea nitrogen tests and other examinations of blood and urine. Those tests are most valuable when samples are taken several days after arrival, by which time initial adjustments to the new environment have been made. Abnormal findings on any of the tests might warrant followup examinations.

Evidence of behavioral adjustment includes decreases in fearful behaviors, increases in friendly behaviors, increases in playfulness, and normal grooming behaviors. Some dogs might not adapt to human handling or the environment and are therefore inappropriate for use in long-term studies. The dealer should be questioned about the sources and histories of such dogs to determine whether additional dogs purchased from that dealer will be similarly distressed. Information on maladaptive canine behavior has been published elsewhere (Scott, 1970).

Many procedures—such as trimming of nails, removal of matted fur, bathing, and teeth-cleaning—can be performed during the conditioning period.

There is no definitive rule about the optimal period for conditioning. The intended use of the dogs, the season, prevalence of canine diseases in the area, and other factors influence the length of the conditioning period. If the dogs are well selected, adequately socialized, immunized, and treated for parasites before delivery, the conditioning period can be reduced. Random-source dogs that have been held for 10 days or more by the dealer usually require at least 21 days of conditioning at the institution before one can be confident that they have adapted fully. Some prefer a minimal conditioning period of 45 days. The importance of humane treatment and proper care during conditioning must be emphasized.

CONTROL OF INFECTIOUS DISEASES

General Considerations

There are three important strategies for controlling canine infectious diseases: examining dogs on arrival and refusing to accept dogs that exhibit

signs of disease, placing all newly acquired dogs in quarantine, and isolating dogs that become sick. Some infectious pathogens to which dogs are susceptible could be introduced into an established colony by new arrivals, especially by random-source dogs, which are commonly unvaccinated. The most common of these pathogens are canine distemper virus (CDV); canine parvovirus (CPV-2); canine herpesvirus (CHV); the respiratory agents canine parainfluenza (PI-2), *Bordetella bronchiseptica*, and *Mycoplasma* spp.; canine adenovirus type 1 (CAV-1, infectious canine hepatitis) and type 2 (CAV-2, tracheobronchitis virus); and canine coronavirus (CCV). An additional problem that warrants careful consideration is the possibility that unvaccinated random-source dogs can harbor rabies virus, which can have a long incubation period (Acha and Szyfres, 1987). Dermatophytosis (ringworm, principally *Microsporum canis* and *M. gypseum*) and canine papillomatosis (warts) can also present problems. Protection against these pathogens is discussed briefly below. Detailed information on canine infectious diseases is available in a number of general references (e.g., Appel, 1987; Barlough, 1988; Greene, 1990).

Quarantine

Quarantine (in this context, the isolation of newly acquired animals until their health status has been evaluated) minimizes the risk of spreading diseases from newly arrived dogs to those already in the colony. In most facilities, the quarantine and conditioning periods overlap. During the quarantine period, most attention is directed to the control of infectious diseases and parasites. Procurement of dogs that are free of infectious diseases and parasites (i.e., conditioned random-source dogs or dogs bred specifically for research) reduces the time necessary for both quarantine and conditioning and might result in more reliable research results. Nonconditioned random-source dogs should be quarantined as a group, and no additional nonconditioned dogs should be introduced into the group.

Quarantine facilities should be designed to provide physical barriers to the spread of infectious diseases (e.g., unidirectional airflow). That is especially important when the research and quarantine facilities are parts of a single building. It is preferable for a quarantine facility to have its own animal-care technicians; however, if this is not possible, quarantined dogs should be cared for last.

Newly arrived dogs should be housed singly to enable veterinarians and technicians to determine which dogs are not eating well, exhibit signs of disease, or are abnormal in other ways. Ideally, dogs are vaccinated by the dealer. If not, they should be vaccinated as soon as possible after arrival against CDV, CPV-2, and CAV-2 (such vaccination also protects against

CAV-1). Vaccination for PI-2 and *B. bronchiseptica* should be considered in institutions where respiratory disease is common. If the dogs are to be vaccinated against leptospirosis and rabies, that is usually done at the same time. If a person is bitten or scratched, the injured area should be cleansed, the person should be referred to appropriate medical personnel, and the dog should be isolated for at least 10 days, as recommended by the National Association of State Public Health Veterinarians (1993).

Research and Breeding Colonies

The major threat to an established colony is that newly introduced dogs might harbor an infectious-disease agent or that personnel might carry such an agent into the colony on their hands or clothing. A regular immunization program, quarantine of nonconditioned random-source dogs, and rigorous sanitation practices will help to protect against infectious agents inadvertently introduced into an established colony. Annual vaccination with a multivalent vaccine is generally recommended, although immunity to CDV and CPV-2 generally persists for at least 3 years. In areas in which respiratory disease is common, frequent vaccination (every 3 months) might be indicated. Frequent vaccination (every 6 months) with leptospira bacterins is recommended in areas in which leptospirosis is endemic or is a proven problem.

Breeding Stock

Some infectious diseases are of special concern in breeding colonies. CHV can remain undetected in a breeding kennel for years. When susceptible, pregnant (usually young) bitches are introduced into the colony, latent CHV manifests itself by causing abortions or fetal or neonatal deaths. A detailed discussion of CHV is available elsewhere (Carmichael and Greene, 1990a).

Canine brucellosis can severely affect reproduction in a breeding kennel. It is also a zoonosis. All dogs purchased for breeding stock should be tested for *Brucella canis* antibodies on arrival and placed in quarantine for at least 1 month, at which time a second brucellosis test should be run. New dogs should not be introduced into a breeding colony unless both tests are negative. An infected dog should not be used for breeding or for long-term studies. Beagles have an unusually high prevalence of brucellosis, although it is occasionally diagnosed in random-source dogs (Carmichael, 1979). For detailed discussions of canine brucellosis see Carmichael (1990) and Carmichael and Greene (1990b).

Pups

CDV and CPV-2 infections are the principal viral diseases that threaten pups during the first 4 months of life, and prevention of these diseases should be the principal objective of an immunization program. Maternal antibody to CDV interferes with the development of an immune response to CDV vaccine; measles vaccine protects against disease but not infection in pups in which maternal antibody is still present (pups about 6-10 weeks old) (Baker, 1970). CDV vaccine should be given to dogs by 14 weeks of age. No vaccines can prevent parvovirus infection in pups during one critical period—that during which they still have maternal antibodies that inhibit the response to vaccination but do not protect against virulent CPV-2 (Carmichael, 1983). Proper management practices are critical in preventing this infection. If a pup does contract the disease, it should be isolated immediately, and rigorous disinfection procedures should be implemented. Diseases caused by adenoviruses and CCV can occur in pups, but they are less common.

It is generally recommended that modified live-virus vaccines be used for immunization, if available. A killed-virus vaccine is used for rabies. A multivalent vaccine that protects against distemper, hepatitis, leptospirosis, and parvovirus and parainfluenza infections can be used. An intranasal vaccine against *Bordetella bronchiseptica*, which causes kennel cough, is generally recommended. Several vaccination regimens have been proposed (Baker et al., 1961; Carmichael, 1983; Swango, 1983); one of them is given in Table 5.1 as a guide, but others are acceptable. The vaccination schedule should be adapted to address the perceived risk of infection.

Pups can be vaccinated with intranasal vaccine against *B. bronchiseptica* at 3-4 weeks of age. Other than that, vaccinating pups less than 6 weeks old is not recommended, because vaccine safety has not been studied in very young pups. Isolation is more important than vaccination in preventing disease in such pups.

TABLE 5.1 A Vaccination Schedule for Pups

Age	Vaccine
6 weeks	CDV or CDV combined with measles and CPV-2
8-10 weeks	CPV-2
12-14 weeks	Multivalent vaccine
16 weeks	CPV-2 (or multivalent vaccine) and rabies

Specific-Pathogen-Free Colonies

Dogs from known matings that have never been exposed to specific infectious agents are called specific-pathogen-free (SPF) for those agents. These dogs are used in infectious-disease and vaccine-development research in which animals are required not only to be free from pathogenic agents, but never to have been exposed, either naturally or through vaccination, to pathogenic agents. It might also be preferable to use SPF dogs in some transplantation studies, because in profound immunosuppression, native and vaccinal viruses (e.g., CDV and CAV-1) might be activated and cause disease (Thomas and Ferrebee, 1961).

The objective in preventing the outbreak of disease in SPF colonies is to isolate, rather than immunize, the dogs. Disease prevention depends on the establishment of physical barriers to preclude the introduction of disease agents, rigorous management practices, and control of personnel movement into and within the facility (Sheffy et al., 1961). Rodents and other pests that can transmit disease mechanically must be excluded. Purpose-bred SPF dogs are available commercially. If bred by the institution, initial breeding stock should be procured from dogs free of latent infectious agents, and all offspring taken by hysterectomy or cesarean section. Embryo-transfer technology offers additional possibilities for SPF colonies. Population immune status should be assessed periodically (at least once a year) by monitoring for antibodies to the common infectious diseases. In the event of an inadvertent infection that would compromise the use of the animals, the colony should be depopulated and re-established.

CONTROL OF PARASITIC DISEASES

Parasites are common in dogs, particularly random-source dogs. They can be found on the skin and hair and in the ears (ectoparasites) and in many internal organs, including the digestive tract, heart, lung, and blood vessels (endoparasites). Specific canine parasites are discussed briefly below; details on life cycles of, treatment for, and prevention or control of these parasites are found elsewhere (Georgi and Georgi, 1992).

Ectoparasites

Ectoparasites include ticks, mites, lice, and fleas. Most can be easily eradicated with insecticides. Three ectoparasites commonly carried by random-source dogs can pose problems if they are not eliminated during quarantine.

- The most damaging is probably the *Rhipicephalus sanguineus* tick. This tick can feed on dogs during all life-cycle stages, and once it enters a facility, it can be expensive to remove.
- Mange caused by *Sarcoptes scabei* is sometimes inadvertently introduced into a facility on a dog that shows no overt signs of dermatosis. This parasite can be a particular problem in dogs that are group-housed or housed in cages or runs that allow the touching of body parts among animals (e.g., through wire-mesh walls). Sarcoptic mange is treated by dipping the affected dogs and all dogs in contact with them in insecticide. It is probably also worthwhile to steam-clean enclosures and floors.
- Fleas are commonly brought into facilities by random-source dogs. The flea life cycle can be disrupted by cleaning enclosures daily to remove developing eggs and larvae. Another strategy is to house dogs in enclosures raised more than 33 cm above the floor. Fleas cannot jump higher than 33 cm, so fleas that fall to or develop on the floor cannot reach the dog to feed.

Additional ectoparasitic infestations that might persist in kennel settings include infestation with ear mites (*Otodectes cynotis*), "walking dandruff" (*Cheyletiella yasguri*), and lice (*Linognathus setosus*, *Trichodectes canis*, and *Heterodoxus spiniger*). The canine nasal mite (*Pneumonyssoides caninum*) can also persist, but it is not known how often infestations with this mite occur in random-source dogs.

To prevent the introduction of skin-dwelling ectoparasites, random-source dogs should be bathed or dipped before they are moved to the housing facility. Their ears should be examined and, if appropriate, treated for ear mites. Mites should be considered as the cause of persistant skin lesions, and appropriate action should be taken to make a correct diagnosis.

All dogs, including random-source and breeding-colony dogs, are probably host to the hair-follicle mite *Demodex canis*. Dogs probably become infected as puppies while nursing. Typically, the infestation is nonpathogenic; in rare instances, the mite causes severe mange. The development of demodectic mange in large numbers of kennel dogs is rare but has occurred. Treatment with topical applications or dips is possible as long as the lesions remain focal, but generalized demodectic mange often indicates some underlying problem (e.g., an inherited susceptibility to demodectic mange or a compromised immune system), and its treatment is difficult or impossible.

Endoparasites

SPF dogs and purpose-bred dogs often host both protozoan and helminthic endoparasites. The protozoa include *Isospora* spp., *Giardia* spp., trichomonads, *Cryptosporidium* spp., *Balantidium* spp., and amebas. The helminths include ascarids (e.g., *Toxocara canis* and *Toxascaris leonina*), *Filaroides*

spp., *Strongyloides stercoralis*, and occasionally hookworms and whipworms. If dogs are housed in a manner that allows mosquitoes access to them, they are also susceptible to infection with heartworm, *Dirofilaria immitis*.

Isospora spp. have direct life cycles (i.e., no intermediate host is required). Oocysts of these coccidia are commonly present in the feces of young dogs raised in colonies, and more than one species can be present in one dog. The oocysts of *I. canis*, *I. ohioensis*, *I. neorivoltos*, and *I. burrowsi* are morphologically similar; however, those of *I. canis* are larger than those of the other three. Clinical signs include increased temperature and diarrhea that is occasionally bloody. Infections usually subside after several days to weeks. Oocyst shedding decreases to low numbers 4 weeks after it begins. Chemoprophylaxis and basic sanitation are necessary to control the infection if it causes problems.

Cryptosporidium is occasionally present in dogs in closed colonies, although it typically does not cause disease. In immunocompetent dogs, the small oocysts of *Cryptosporidium* are shed in low numbers, if at all, for a limited period; however, in immunosuppressed or immunocompromised dogs, *Cryptosporidium* can cause fatal disease. There is no proven method of chemoprophylaxis or treatment, but routine sanitation procedures, accompanied by regular steam cleaning of areas that might be contaminated, will assist in reducing exposure to oocysts.

Giardia canis is commonly present in both purpose-bred and SPF dogs. The prevalence is high in pups and decreases with age. The organism is spread between dogs by the fecal-oral transmission of resistant cysts. Typically, pups are infected with *Giardia* and one or more species of *Isospora*; however, the infection usually causes little or no disease. As dogs mature, the number of organisms decreases. As with *Isospora*, chemoprophylaxis and basic sanitation are the most effective means of controlling *Giardia*.

Trichomonas canistomae is a commensal organism present in the mouths of many dogs. It has no cyst stage and is transmitted between dogs by direct oral contact. There is usually no need for treatment. Species of *Trichomonas* and *Pentatrichomonas* are present in the large intestines of many laboratory-reared dogs. None of these species has a cyst stage; transmission is by the fecal-oral route. These organisms are sometimes observed in diarrheic feces in very large numbers, but they are usually not the cause of the diarrhea. Treatment is available but usually not necessary.

Balantidium coli, a large ciliated parasite that is rarely found in dogs, and *Entamoeba coli* and *E. histolytica*, smaller ameboid parasites, are transmitted by cysts passed in the feces. These parasites are present in the large bowel. Their life cycles are similar to that of *Giardia*, and once they are established in a colony, they are easily perpetuated.

The ascaridoid nematode (roundworm), *Toxocara canis*, is a common parasite of the small intestines of dogs, even in closed breeding colonies.

The parasite is transmitted from bitches to pups in utero, and pups begin to shed eggs in their feces a few weeks after birth. Once the eggs enter the environment, they require about 2 weeks to become infectious; they are very resistant to environmental extremes of heat, cold, and humidity. Pups should be treated soon after birth and several times during early life to prevent the development of adult roundworms from the stages obtained prenatally. Control measures should include steam cleaning of floors and disinfection of floors with a 1:4 (20 percent) solution of chlorine bleach. Adult dogs can have larvae in their tissues whether or not they are shedding eggs in their feces. It is possible to determine whether a dog has ever been infected by measuring antibody concentrations, and dogs that are *Toxocara canis*-naive are available commercially.

The other canine ascaridoid, *Toxascaris leonina*, has a direct life cycle and does not infect pups transplacentally. The eggs of this parasite develop more rapidly than those of *Toxocara canis* but are just as resistant to extremes of heat, cold, and humidity. *Toxascaris leonina* is commonly present in the small intestines of older purpose-bred and SPF dogs, but it is not known how the cycle is maintained in these colonies. Control and treatment are the same as those used for *Toxocara canis*.

Filaroides hirthi is present in the lung parenchyma of many purpose-bred and SPF dogs. The lung lesions caused by the parasite can confuse histopathologic evaluations in toxicologic experiments. The life cycle is direct, and infective larvae are transmitted between dogs by oral or fecal-oral contact. Immunosuppressed dogs can become seriously ill as a result of auto-reinfection that leads to heavy parasite burdens. Infections can be treated, but control is difficult because fecal assays are insensitive. Therefore, all dogs in a contaminated room must be treated, not just those with positive fecal tests. Proper sanitation is helpful, but the larvae do not persist for long periods in the environment.

Strongyloides stercoralis lives as a parthenogenetic female in the mucosa of the canine small intestine. Larvae develop to the infective stage 4-5 days after they are passed in feces. Transmission is by penetration of the skin by infective-stage larvae and by passage of tissue-dwelling larvae in the milk of lactating bitches. Immunosuppressed or immunocompromised dogs can develop severe disease as a result of auto-reinfection. *S. stercoralis* is also transmissible to humans. Although treatment is available, elimination of the parasite from a breeding colony is difficult because it is not certain that transmammary transmission can be interrupted by chemotherapeutic measures. Routine removal of feces and cleaning of cage or pen floors reduce transmission.

Adult hookworms live in the small intestine, where they cause blood loss and anemia. The hookworms *Ancylostoma caninum* and *A. braziliense*, like *S. stercoralis*, are transmitted through the milk or by larval penetration

of the skin. However, infective-stage larvae are more likely to develop in soil than on a moist cage bottom fouled with feces, and transmission is more likely when dogs are housed outside on such surfaces as gravel or sand. Unlike dogs infected with *S. stercoralis*, dogs infected with hookworms often show signs of overt disease, characterized by bloody diarrhea. In addition, hookworm eggs are much easier to detect in feces than are *S. stercoralis* larvae. Those differences and the dissimilarity of conditions required for larval development make it much less likely that hookworms will persist undetected in a colony. The hookworm *Uncinaria stenocephala*, which is present in more temperate climates, is transmitted mainly by larval ingestion; skin penetration and transmission in milk are uncommon. Thus, *U. stenocephala* is less likely to be perpetuated in a closed colony.

Whipworms, *Trichuris vulpis*, live in the cecums and colons of dogs and cause large bowel disease that can produce bloody stools. The life cycle of this parasite is direct. Eggs are passed in feces and take several weeks to become infectious. They are highly resistant to environmental extremes, so contamination is very peristent if eggs get into the soil of earthen-floored runs. Dogs become infected by ingesting the infective eggs on soil-contaminated items. In the dog, the worms take about 3 months to develop to the adult stage, and reinfection is common. Treatment is available but often has to be repeated.

The filarioid nematode *Dirofilaria immitis* causes heartworm disease. It is transmitted between dogs by the bite of a mosquito. The prepatent period (the time between the inoculation of maturing forms by the mosquito and the first appearance of microfilariae in the host's blood) is slightly more than 6 months. The infection is often manifested as cardiopulmonary disease accompanied by respiratory distress and right-sided heart enlargement. In dogs with patent disease, infections can be diagnosed by demonstrating microfilariae in the blood; however, some infected dogs do not have circulating microfilariae (Glickman et al., 1984.). When it is important to ascertain that dogs are heartworm-free, serum or plasma can be examined with antigen-detection tests. Treatment for heartworm infection is generally precluded by its high cost, the stress it causes the dog, the length of time necessary for recovery, and the possibility of residual pathologic changes in the cardiovascular system.

Where *D. immitis* is enzootic, dogs given access to outside runs should be protected by chemical prophylaxis. If dogs cannot be placed on chemical prophylaxis, because of a study design or for other reasons, they can be protected by enclosing the outside kennels with screening.

In addition to infection with the same parasites found in purpose-bred and SPF dogs, random-source dogs are likely to be infected with parasites that are relatively rare or that require intermediate hosts as part of their life cycles. If the intermediate hosts are uncommon (e.g., snails, then crayfish

for the lung fluke *Paragonimus kellicotti*), there is little chance that the infection will be maintained in a kennel. However, if the intermediate host is commonly present around dogs (e.g., fleas for the tapeworm *Dipylidium caninum*), the parasite will probably persist in the facility as long as the intermediate host is present. Additional parasites that can be found in random-source dogs include the tapeworm *Taenia* spp. (intermediate hosts, mammals), the intestinal fluke *Alaria canis* (snails, then frogs), the esophageal nematode *Spirocerca lupi* (beetles), and the stomach nematode *Physaloptera* spp. (beetles).

Two parasites that are found rarely in random-source dogs, *Echinococcus* spp. and *Trypanosoma cruzi*, are important because they cause zoonoses. Larval stages of the canine tapeworms *Echinococcus granulosus* and *E. multilocularis* can be transmitted to humans in contaminated feces and cause unilocular and multilocular hydatid disease, respectively. Eggs of *Echinococcus* spp. are infectious when passed in feces and cannot be distinguished morphologically from eggs of taeniid tapeworms. *E. granulosus* is present in focal areas of the United States; *E. multilocularis* is present in the far northern continental United States, Alaska, and Canada. *Trypanosoma cruzi*, which is present in the southern United States, is a hemoflagellated protozoan that can infect the blood and tissues of opossums, armadillos, dogs, humans, and other mammals. Humans are infected by accidental self-inoculation with blood products from an infected animal. People handling dogs from areas where *Echinococcus* spp. and *T. cruzi* are enzootic should be made aware that such infections, although rare, are possible and can be associated with life-threatening conditions in humans.

Three other uncommon canine pathogens, all requiring arthropod vectors, have occasionally been diagnosed in dog facilities: *Leishmania* spp., *Babesia* spp., and *Ehrlichia canis*. The clinical signs caused by these pathogens are often poorly deliniated, so they can be harder to diagnose than common helminth infections.

Cutaneous and visceral leishmaniasis, caused by infections with various species of *Leishmania*, have been reported in both kennels and research colonies. The organism is typically transmitted between dogs by the bite of a phlebotomine sandfly, although the mode of transmission in the reported cases is not certain. Diagnosis is typically made by identifying the organisms histopathologically or serologically. Treatment is difficult but possible.

Babesiosis, caused by *Babesia canis* or *Babesia gibsoni*, can be introduced into colonies or kennels through an infected dog, an infected tick, or a blood transfusion. Once it is in an establishment, horizontal transmission typically occurs through exposure to infected blood that is not handled properly or through ticks, particularly *Rhipicephalus sanguineus*. Dogs with babesiosis display regenerative anemia, i.e., the bone marrow remains

functional, and increased numbers of immature erythrocytes appear in the blood. The disease can be diagnosed by demonstrating the organisms in erythrocytes on stained blood films. Treatment is difficult, and drugs routinely used in parts of the world where babesiosis is common are not easily obtained in the United States.

Transmission of ehrlichiosis, a rickettsial infection caused by *Ehrlichia canis*, is similar to transmission of babesiosis. Signs of ehrlichiosis in dogs include fever, anorexia, epistaxis (nosebleeds), and reduced kidney function. Diagnosis is made serologically or by demonstrating the presence of the organism in blood smears. Treatment can alter the course of the disease but does not prevent an affected dog from becoming a carrier of the infection.

Good sanitation is probably the major means for controlling endoparasites in a dog facility. In facilities that house purpose-bred or SPF dogs, feces from healthy animals of different ages should be examined periodically for subclinical helminth or protozoan infections. Fecal and blood examinations can be used to screen random-source dogs for parasites on arrival at the facility. To prevent the introduction of helminth parasites into a facility, random-source dogs might be treated for some infections with an anthelminthic. A practical choice would be a broad-spectrum anthelminthic that is active against both nematodes and tapeworms.

RECOGNITION AND ALLEVIATION OF PAIN AND DISTRESS

Recognition of Distress Induced by Pain

Distress can be defined as "an aversive state in which an animal is unable to adapt completely to stressors and the resulting stress . . ." (NRC, 1992, p. 4). Scientists have legal, ethical, and humane obligations to minimize distress in experimental animals. Moreover, there is a pragmatic reason to minimize distress. Unless a stressor (such as pain) is the subject of the experiment, distressed animals might provide erroneous data (Amyx, 1987). Pain is an important cause of distress and is usually produced by disease, injury, or surgery.

Table 5.2 lists some of the signs of pain in dogs. Dogs usually respond to acute pain by vocalizing and by protecting or guarding the area of perceived pain. Signs include withdrawing, attempting to bite if touched, and adopting unusual postures (e.g., the laterally flexed position commonly adopted after lateral thoracotomy). Low-grade pain can produce restlessness. Severe pain, especially if chronic, usually makes dogs appear depressed and lethargic. The decrease in activity can be accompanied by one or more of the following: shivering, inappetence, panting, howling, or whining.

The *U.S. Government Principles for Utilization and Care of Vertebrate*

TABLE 5.2 Signs of Pain in Dogs[a]

Sign	Comment
Guarding	Attempting to protect or move painful part away (e.g., hunched position after celiotomy or laterally flexed position after lateral thoracotomy), attempting to bite
Vocalization	Whining or whimpering when touched or forced to use affected part
Mutilation	Licking, biting, scratching, shaking, or rubbing affected part
Restlessness	Pacing, lying down and getting up, or shifting weight
Recumbency	For unusual length of time
Depression	Inappetence, reluctance to move, or difficulty in rising
Pallor	Pale mucous membranes, probably a result of vasoconstriction caused by an increase in sympathetic tone

[a]Adapted from Soma, 1987; printed with permission of the author, the American Association for Laboratory Animal Science, and the Scientists Center for Animal Welfare.

Animals Used in Testing, Research, and Training (published in NRC, 1985) states that "unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals." This statement makes it clear that most surgical interventions must be accompanied by adequate anesthesia and suitable postoperative analgesia. Table 5.3 lists the degree and duration of pain that can be expected after surgery on various parts of a dog's body. Although pain thresholds are similar between individuals and even between species, pain tolerance varies widely. Therefore, each dog should be observed and treated as an individual in determining the need to administer analgesics.

Alleviation of Pain

Anesthetics

General anesthesia is the most important way of alleviating pain associated with surgery, and several textbooks contain detailed descriptions of acceptable techniques for inducing general anesthesia in dogs (Booth, 1988a; Hall and Clarke, 1991; Lumb and Jones, 1984; Muir and Hubbell, 1989; Short, 1987). Inhaltant agents (e.g., isoflurane, methoxyflurane, and halothane) are often best for this purpose because they allow close regulation of the duration and depth of anesthesia and rapid and controlled reversibility. However, special equipment is required for administering them. Nitrous oxide is not a general anesthetic in dogs and should be used only as an adjunct to other, more potent anesthetics.

General anesthesia can also be provided with injectable drugs, such as barbiturates (e.g., thiamylal, thiopental, and pentobarbital), propofol, or Telazol

TABLE 5.3 Signs, Degree, and Length of Surgically Produced Pain[a]

Surgical Site	Signs of Pain	Degree of Pain	Length of Pain
Head, eye, ear, mouth	Attempts to rub or scratch; self-mutilation; shaking; reluctance to eat, drink, or swallow; reluctance to move	Moderate to high	Intermittent to continual
Rectal area	Rubbing, licking, biting, abnormal bowel movement or excretory behavior	Moderate to high	Intermittent to continual
Bones	Reluctance to move, lameness, abnormal posture, guarding, licking, self-mutilation	Moderate to high: upper part of axial skeleton (humerus, femur) especially painful	Intermittent
Abdomen	Abnormal posture (hunched), anorexia, guarding	Not obvious to moderate	Short
Thorax	Reluctance to move, respiratory changes (rapid, shallow), depression	Sternal approach, high; lateral approach, slight to moderate	Continual
Spine, cervical	Abnormal posture of head and neck, reluctance to move, abnormal gait-"walking on eggs"	Moderate to severe	Continual
Spine, thoracic or lumbar	Few signs, often moving immediately	Slight	Short

[a]Based on observations of dogs. Reprinted from NRC, 1992.

(a mixture of tiletamine and zolazepam). Each injectable drug has properties that determine its duration of action and the route by which it is best administered. Ketamine is used as an anesthetic but its effectiveness as an analgesic for visceral pain is disputed (Booth, 1988b; Hughes and Lang, 1983). It should be used in combination with another analgesic agent when visceral pain is expected. It can also induce seizure-like activity in dogs unless it is used in conjunction with another drug, such as diazepam, acepromazine, or xylazine. Chloralose and urethane are injectable anesthetics that have been used in some experiments; however, chloralose alone is a poor anesthetic that produces little analgesia unless it is combined with an opiate such as morphine (Rubal and Buchanan, 1986), or a short-acting anesthetic (Flecknell, 1987). Urethane is mutagenic and carcinogenic (Auerbach, 1967; Mirvish, 1968); it should be used with caution and only for nonsurvival surgery.

Neuromuscular blocking agents (e.g., succinylcholine, atracurium, curare,

gallamine, pancuronium, and vecuronium) have no anesthetic or analgesic properties. They must not be used alone for surgical restraint, although they may be used in conjunction with anesthetic doses of general anesthetic drugs (NRC, 1985).

Local anesthetics (e.g., lidocaine, mepivacaine, and bupivacaine) act to disrupt nerve conduction temporarily. When applied around a nerve, they produce analgesia in the region served by that nerve. However, these drugs have no depressant effect on the brain; dogs undergoing procedures under local anesthesia usually must be restrained physically or chemically (e.g., with tranquilizers or sedatives). Specific techniques for regional anesthesia are described in several texts (Hall and Clarke, 1991; Lumb and Jones, 1984; Muir and Hubbell, 1989; Skarda, 1987; Soma, 1971). Local anesthetics alone are ordinarily used for only the most minor of surgical interventions; but they can be given either intrathecally or epidurally (usually via the lumbosacral space) to provide segmental anesthesia of caudal body parts sufficient for major surgery (e.g., celiotomy) (Skarda, 1987).

Analgesics

Opioid analgesics are compounds that act at specific opioid receptor sites in the central nervous system to produce analgesia. Table 5.4 lists some of these compounds. They are not general anesthetics, but can be used for surgery when combined with other appropriate drugs (NRC, 1992). Opioid analgesics (e.g., oxymorphone) can be injected epidurally to control postsurgical pain for extended periods with minimal systemic effects (Popilskis et al., 1991).

Opioid agonists have been combined with tranquilizers to produce so-called neuroleptanalgesic combinations (e.g., a mixture of fentanyl and droperidol known by the trade name Innovar-Vet and produced by Pitman Moore, Mundelein, Ill.). Such combinations are capable of producing a state that

TABLE 5.4 Opioid Analgesics Used in Dogs[a]

Drug	Dose (mg/kg)	Route[b]
Buprenorphine	0.01-0.2	IV, IM
Butorphanol	0.2-0.5	IV, IM
Fentanyl	0.04	IV, IM
Meperidine	2.0-6.0	IM
Morphine	0.5-1.0	SC
Oxymorphone	0.2-0.4	IV, IM

[a]Data from Harvey and Walberg, 1987.
[b]IV = intravenous; IM = intramuscular; SC = subcutaneous

sufficiently resembles general anesthesia to permit some surgical procedures (Muir and Hubbell, 1989; Soma and Shields, 1964). Xylazine, which is classified as a sedative, has analgesic properties because of its action on central alpha-2 receptor sites.

The nonsteroidal anti-inflammatory analgesics include acetaminophen, aspirin, flunixin, and ibuprofen. These drugs inhibit prostaglandin synthesis. They are ordinarily used to relieve the acute or chronic pain associated with inflammation and have little place in the management of severe or acute pain that is not associated with inflammation (NRC, 1992).

Recognition of Distress Not Induced by Pain

Signs of distress caused by stressors other than pain include changes in behavior (e.g., unexpected aggression), maladaptive behaviors (e.g., stereotypies), and physical changes (e.g., weight loss). Experienced and attentive animal caretakers are of the utmost importance in early recognition of signs of distress. Changes in biochemical measurements (e.g., plasma cortisol concentration) can also help in recognition of distress.

Alleviation of Distress Not Induced by Pain

Distress caused by stressors other than pain is often related to husbandry practices. Understanding and meeting dogs' social and physical needs will minimize or prevent such distress (NRC, 1992).

Phenothiazine tranquilizers, such as acepromazine (0.03-0.05 mg/kg intravenously or intramuscularly, 1.0-3.0 mg/kg by mouth), are useful as preanesthetic drugs because they make unruly animals more tractable, reduce the doses of anesthetic drugs necessary to maintain anesthesia, and make recovery from anesthesia smoother. However, they can have unpredictable effects and cause some animals to become excited rather than tranquil (Voith, 1984). The phenothiazines have minimal antianxiety effects, and they are not the drugs of choice for decreasing fearful reactions (Marder, 1991).

Alpha-2 agonists, such as xylazine (0.3-1.0 mg/kg intravenously, 0.5-2.0 mg/kg intramuscularly), have many of the advantages of the phenothiazines and are also good analgesics (Gleed, 1987). However, they can cause serious cardiovascular depression, hyperglycemia, and depressed thermoregulation, which can be reversed with yohimbine if necessary (Denhart, 1992).

Benzodiazepines, such as diazepam (0.1-0.5 mg/kg intravenously, 0.3-0.5 mg/kg intramuscularly) are often used as adjuncts to injectable anesthetic drugs, such as the barbiturates and ketamine, because they reduce the dose necessary to produce anesthesia and provide muscle relaxation (Gleed, 1987). Diazepam (Valium) is also used alone to treat seizures. Like the

phenothiazines, the benzodiazepines have an excitatory effect on some animals. Because they are the drugs of choice for the treatment of fearful behaviors (Marder, 1991), especially fear of people (Hart, 1985), they can be useful in reducing distress in unsocialized dogs. However, the benzodiazepines must be used with care in dogs that display fear-motivated aggression. Decreasing the fear might make such dogs more likely to attack (Marder, 1991).

SURGERY AND POSTSURGICAL CARE

Surgery in dogs should be performed in accordance with the tenets in the *Guide* (NRC, 1985). The requirements for minor and nonsurvival surgical procedures are less stringent than those for major survival surgical procedures.

Personnel performing surgical procedures must be adequately trained. Facilities for performing surgical procedures should be available as outlined in the *Guide* (NRC, 1985). The successful practice of survival surgery requires strict adherence to aseptic surgical technique, as well as provision of adequate postoperative care and analgesia for the experimental subject. Aseptic techniques also have some value in major nonsurvival surgical procedures (Slattum et al., 1991). Generally, only healthy conditioned or purpose-bred dogs should be used for survival surgery. Familiarizing the dog with the laboratory environment can assist investigators in identifying intractable subjects and can be beneficial in decreasing postoperative stress.

Presurgical Preparation

Dogs should be surgically prepared by careful shaving to remove all hair from the surgical field. Shaving reduces contamination of the wound and avoids delays in healing that can occur if hair becomes matted in the incision. If a thermal cautery is to be used, an area should also be shaved for placement of a ground lead. Adherent grounding pads are available. The surgical field should be thoroughly cleaned with Betadine (povidone-iodine) or another appropriate surgical scrubbing material. Betadine sterile solution or other appropriate preparation should be applied to the entire field and allowed to dry. Underpadding used to absorb such solutions can be flammable and should be removed before surgery.

All surgical instruments and chronic instrumentation must be sterilized with steam (autoclaving) or gas (ethylene oxide with proper poststerilization aeration time). Cold chemical sterilization is appropriate for minor surgical procedures, but exposure time must be adequate, and the instruments must be thoroughly rinsed in sterile saline before they come into contact with body tissues. All items should be packaged for sterilization in such a way

that they can be opened and positioned for use without compromising sterility. Investigators should follow standard surgical practices: donning surgical caps and masks, scrubbing, and donning surgical gowns and gloves. Sterile drapes should be positioned on the dog to define the surgical field. During the course of surgery, procedures for preserving sterility should be strictly followed.

Generally, dogs should be treated with the appropriate preanesthetic medications (e.g., tranquilizers and atropine) to provide a degree of sedation and facilitate handling. General anesthesia is reviewed in the section "Alleviation of Pain" (see pages 64-67); the type used depends on the type and duration of the surgical procedure. The adequacy of anesthesia can be assessed by the absence of the eyelid reflex and by the lack of withdrawal in response to painful stimuli (e.g., toe pinch). Insertion of a cuffed endotracheal tube will ensure patency of the respiratory tract.

The physiologic status of dogs under general anesthesia should be assessed by monitoring such parameters as pulse rate, systemic blood pressure, and respiratory rate. Electrocardiography can be used to monitor the status of the heart. A heating pad is useful for maintaining body temperature. If inhalant anesthetics are used, the anesthetized dog should be ventilated (tidal volume, 15-20 ml/kg; respiratory rate, 13-20 breaths/minute), and carbon dioxide should be monitored. Respiratory rate, tidal volume, and inspiratory-expiratory ratio can be adjusted to achieve acceptable end-tidal carbon dioxide (38-40 torr) and blood oxygen saturation greater than 90 percent.

An intravenous catheter should be placed in the cephalic vein to provide a continuous intravenous drip (e.g., of lactated Ringer's solution) for volume replacement and to ensure rapid access to the circulatory system. Depending on the situation, antibiotics can be administered through the catheter or intramuscularly. There is evidence that giving antibiotics during the 2 hours before surgery is more beneficial than giving them either during or after surgery (Classen, 1992).

Postsurgical Care

Appropriate analgesics should be administered for postoperative pain, as needed (see pp. 66-67 and NRC, 1992). Surgical wounds and sites of instrument entry into the body should be cleaned and treated daily (e.g., with 0.3 percent hydrogen peroxide or dilute Betadine solution). Topical antibiotics (e.g., bacitracin ointment) can be applied. Surgical dressings should be changed every day.

Basic biologic functions—including urination, defecation, and appetite—are good indicators of a dog's overall physical well-being. These are easy to observe and should be monitored regularly and often. Followup clinical

examinations and laboratory tests can be used to identify specific problems. Appropriate supportive care should be provided as needed.

A commonly used experimental protocol involving major survival surgery in the dog is the implantation of instruments that allow physiologic measurements over a long period while the dog is conscious. The dog is particularly suitable for this type of protocol because of its size, its equable temperament, and the close parallelism of its physiologic functions with those of humans. Strict adherence to the recommendations above will minimize confounding effects.

EUTHANASIA

Euthanasia is a method of killing an animal rapidly and painlessly (NRC, 1985). It should be carried out by trained personnel following current guidelines established by the American Veterinary Medical Association (AVMA) Panel on Euthanasia (AVMA, 1993 et seq.; NRC, 1985) The method used must produce rapid unconsciousness and subsequent death without evidence of pain or distress, or the animal must be anesthetized before being killed (9 CFR 1.1). The method used should also be safe for attending personnel, be easy to perform, and cause death without producing changes in tissues that might interfere with necropsy evaluation. Methods of euthanasia recommended by the AVMA Panel on Euthanasia (AVMA, 1993) are discussed below.

Injection of Lethal Substances

Injection of a lethal substance is probably the most suitable method for euthanatizing laboratory dogs. It usually involves the intravenous injection of a large dose of a barbiturate anesthetic, such as pentobarbital (more than 100 mg/kg). The advantage of this method is that the animal is anesthetized within seconds and does not undergo the pain or distress that might be associated with later respiratory and cardiac arrest. In fact, cardiac arrest can be delayed for many minutes after the onset of anesthesia; therefore, cardiotoxins (e.g., large doses of dibucaine) are sometimes used to hasten death (Wallach et al., 1981). Unruly or aggressive dogs should be sedated or tranquilized to facilitate the restraint necessary for smooth intravenous injection. Intravenous injection is the preferred route of administration because venipuncture is easily performed on most dogs by trained, experienced personnel. Injection outside the circulatory system is less reliable, is potentially painful, and almost invariably produces a slow onset of action.

Injectable drugs—such as magnesium sulfate, potassium chloride, and neuromuscular blocking agents (e.g., atracurium, curare, gallamine, pancuronium, succinylcholine, and vecuronium)—may be used (Bowen et al., 1970;

Hicks and Bailey, 1978); however, the dogs must be in a deep plane of anesthesia before drug administration (AVMA, 1993). Strychnine and nicotine are not suitable for euthanasia, because their stimulant properties might cause distress even in anesthetized animals.

Inhalation Methods

Overdose of a potent inhalant anesthetic (e.g., halothane and isoflurane) is satisfactory for performing euthanasia on dogs and is particularly appropriate for young dogs, in which venipuncture can be difficult. Anesthetic vapors tend to be irritating; therefore, the animals should be tranquilized first. If anesthetic vapors are used, a system for scavenging excess vapor is necessary to comply with federal guidelines on anesthetic-vapor pollution (CDC, 1977). Ether, unlike most contemporary inhalant anesthetics, is flammable and explosive; therefore, its use is not recommended.

Carbon monoxide and carbon dioxide both cause death by hypoxia. Carbon monoxide is impractical in most instances because of the risk to operators and the complexity of the equipment to administer it. Carbon dioxide has anesthetic properties and can be used for euthanasia (Carding, 1968; Leake and Waters, 1929); however, unless the chamber is well designed and used properly, dogs can become distressed before becoming unconscious. Hypoxia is not satisfactory for euthanatizing pups because young animals tolerate hypoxia better than older dogs and can survive for more than 30 minutes (Glass et al., 1944).

Physical Methods

Exsanguination is acceptable for euthanasia; however, the dog must be anesthetized because the decreasing blood flow causes anxiety and autonomic stimulation (Gregory and Wotton, 1984). Electrocution is considered a humane method of euthanasia, provided that sufficient current passes through the animal's brain to produce unconsciousness before or coincidentally with the onset of cardiac arrest. However, this method of euthanasia is not practical in most laboratories because of the danger to personnel (AVMA, 1993; Roberts, 1954; Warrington, 1974). Decapitation of pups is not recommended by the AVMA Panel on Euthanasia (1993).

Human Considerations

Euthanasia of dogs or any other animals can be stressful for the personnel performing the procedure. The degree of distress experienced by people observing or performing euthanasia depends on their backgrounds, personal philosophies, and ethical views on the use of animals in research (Arluke,

1988). People often transfer to the death of animals their unpleasant reactions to human death, and their responses to euthanasia can be magnified when strong bonds exist between them and the dogs being killed (e.g., strong bonds often develop between animal-care personnel and seriously ill canine models that require a great deal of care and rely totally on their human guardians). The stress experienced can be manifested as absenteeism, belligerence, careless and callous handling of animals, and high turnover rate. To be responsive to those concerns, institutional officials and supervisors should be aware of and sensitive to the issues and should provide opportunities for individual and group discussion and support and for educational programs that furnish factual information about euthanasia and teach stress-management and coping skills (NRC, 1991).

REFERENCES

Acha, P. N., and B. Szyfres. 1987. Rabies. Pp. 425-449 in Zoonoses and Communicable Diseases Common to Man and Animals, 2d ed. Scientific Pub. No. 503. Washington, D.C.: Pan American Health Organization.

Amyx, H. L. 1987. Control of animal pain and distress in antibody production and infectious disease studies. J. Am. Vet. Med. Assoc. 191:1287-1289.

Appel, M. J., ed. 1987. Virus Infections of Carnivores. Amsterdam: Elsevier Science Publishers. 500 pp.

Arluke, A. B. 1988. Sacrificial symbolism in animal experimentation. Object or Pet? Anthrozoös 2(2):98-117.

Auerbach, C. 1967. The chemical production of mutations. Science 158:1141-1147.

AVMA (American Veterinary Medical Association). 1993. 1993 Report of the AVMA Panel on Euthanasia. J. Am. Vet. Med. Assoc. 202:229-249.

Baker, J. A. 1970. Measles vaccine for protection of dogs against canine distemper. J. Am. Vet. Med. Assoc. 156:1743-1746.

Baker, J. A., D. S. Robson, L. E. Carmichael, J. H. Gillespie, and B. Hildreth. 1961. Control procedures for infectious diseases of dogs. Proc. Anim. Care Panel 11:234-244.

Barlough, J. E., ed. 1988. Manual of Small Animal Infectious Diseases. New York: Churchill Livingstone. 444 pp.

Booth, N. H. 1988a. Section 4: Drugs acting on the central nervous system. Pp. 153-405 in Veterinary Pharmacology and Therapeutics, 6th ed., N. H. Booth and L. E. McDonald, eds. Ames: Iowa State University Press.

Booth, N. H. 1988b. Intravenous and other parenteral anesthetics. Pp. 212-274 in Veterinary Pharmacology and Therapeutics, 6th ed., N. H. Booth and L. E. McDonald, eds. Ames: Iowa State University Press.

Bowen, J. M., D. M. Blackmon, and J. E. Haevner. 1970. Effect of magnesium ions on neuromuscular transmission in the horse, steer, and dog. J. Am. Vet. Med. Assoc. 157:164-173.

Carding, A. H. 1968. Mass euthanasia of dogs with carbon monoxide and/or carbon dioxide; preliminary trials. J. Small Anim. Pract. 9:245-259.

Carmichael, L. E. 1979. Brucellosis (*Brucella canis*). Pp. 185-194 in CRC Handbook Series in Zoonoses, vol. 1, J. H. Steele, ed. Boca Raton, Fla.: CRC Press.

Carmichael, L. E. 1983. Immunization strategies in puppies—why failures? Compend. Contin. Educ. Practicing Vet. 5:1043-1051.

Carmichael, L. E. 1990. *Brucella canis*. Pp. 335-350 in Animal Brucellosis, K. Nielsen and J. R. Duncan, eds. Boca Raton, Fla.: CRC Press.

Carmichael, L. E., and C. F. Greene. 1990a. Canine herpesvirus infection. Pp. 252-258 in Infectious Diseases of the Dog and Cat, C. E. Greene, ed. Philadelphia: W. B. Saunders.

Carmichael, L. E., and C. E. Greene. 1990b. Canine brucellosis. Pp. 573-584 in Infectious Diseases of the Dog and Cat, C. E. Greene, ed. Philadelphia: W. B. Saunders.

CDC (Centers for Disease Control). 1977. Criteria for a Recommended Standard Occupational Exposure to Waste Anesthetic Gases and Vapors. HEW Pub. No. NIOSH 77-140. Washington, D.C.: U.S. Department of Health, Education, and Welfare. 194 pp. Available by interlibrary loan from the CDC Information Center, M/S C04, Atlanta, GA 30333.

Classen, D. C., R. S. Evans, S. L. Pestotnik, S. D. Horn, R. L. Menlove, and J. P. Burke. 1992. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. N. Eng. J. Med. 326:281-286.

Denhart, J. W. 1992. Xylazine reversal with yohimbine. Pp. 194-197 in Current Veterinary Therapy. XI. Small Animal Practice, R. W. Kirk and J. D. Bonagura, eds. Philadelphia: W. B. Saunders.

Flecknell, P. A. 1987. Special techniques. Pp. 59-74 in Laboratory Animal Anaesthesia. An Introduction for Research Workers and Technicians. London: Academic Press.

Georgi, J. R., and M. E. Georgi. 1992. Canine Clinical Parasitology. Philadelphia: Lea & Febiger. 227 pp.

Glass, H. G., F. F. Snyder, and E. Webster. 1944. The rate of decline in resistance to anoxia of rabbits, dogs and guinea pigs from the onset of viability to adult life. Am. J. Physiol. 140:609-615.

Gleed, R. D. 1987. Tranquilizers and sedatives. Pp. 16-27 in Principles & Practice of Veterinary Anesthesia, C. E. Short, ed. Baltimore: Williams & Wilkins.

Glickman, L. T., R. B. Grieve, E. B. Breitschwerdt, M. Mika-Grieve, G. J. Patronek, L. M. Domanski, C. R. Root, and J. B. Malone. 1984. Serologic pattern of canine heartworm (*Dirofilaria immitis*) infection. Am. J. Vet. Res. 45:1178-1183.

Greene, C. E., ed. 1990. Infectious Diseases of the Dog and Cat. Philadelphia: W. B. Saunders. 971 pp.

Gregory, N. G., and S. B. Wotton. 1984. Time to loss of brain responsiveness following exsanguination in calves. Res. Vet. Sci. 37:141-143.

Hall, L. W., and K. W. Clarke. 1991. Veterinary Anaesthesia, 9th ed. London: Bailliere Tindall. 410 pp.

Hart, B. L. 1985. Behavioral indications for phenothiazine and benzodiazepine tranquilizers in dogs. J. Am. Vet. Med. Assoc. 186:1192-1194.

Harvey, R. C., and J. Walberg. 1987. Special considerations for anesthesia and analgesia in research animals. Pp. 380-392 in Principles & Practice of Veterinary Anesthesia, C. E. Short, ed. Baltimore: Williams & Wilkins.

Hicks, T., and E. M. Bailey, Jr. 1978. Succinylcholine chloride as a euthanatizing agent in dogs. Am. J. Vet. Res. 39:1195-1197.

Hoskins, J. D. 1990. Veterinary Pediatrics: Dogs and Cats from Birth to Six Months. Philadelphia: W. B. Saunders. 556 pp.

Hughes, H. C., and C. M. Lang. 1983. Control of pain in dogs and cats. Pp. 207-216 in Animal Pain: Perception and Alleviation, R. L. Kitchell and H. H. Erickson, eds. Bethesda, Md.: American Physiological Society.

Kaneko, J. J., ed. 1989. Clinical Biochemistry of Domestic Animals, 4th ed. San Diego: Academic Press. 932 pp.

Leake, C. D., and R. M. Waters. 1929. The anesthetic properties of carbon dioxide. Curr. Res. Anesth. Analg. 8:17-19.

Loeb, W. F., and F. W. Quimby, eds. 1989. The Clinical Chemistry of Laboratory Animals. New York: Pergamon Press. 519 pp.

Lumb, W. V., and E. W. Jones. 1984. Veterinary Anesthesia, 2d ed. Philadelphia: Lea & Febiger. 693 pp.

Marder, A. R. 1991. Psychotropic drugs and behavioral therapy. Vet. Clin. N. Am. 21(2):329-342.

Mirvish, S. S. 1968. The carcinogenic action and metabolism of urethan and N-hydroxyurethan. Adv. Cancer Res. 11:1-42.

Muir, W. W., III, and J. A. E. Hubbell. 1989. Handbook of Veterinary Anesthesia. St. Louis: C. V. Mosby. 340 pp.

National Association of State Public Health Veterinarians. 1993. Compendium of animal rabies control, 1993. J. Am. Vet. Med. Assoc. 202:199-204.

NRC (National Research Council), Institute of Laboratory Animal Resources, Committee on Care and Use of Laboratory Animals. 1985. Guide for the Care and Use of Laboratory Animals. NIH Pub. No. 86-23. Washington, D.C.: U.S. Department of Heath and Human Services. 83 pp.

NRC (National Research Council), Institute of Laboratory Animal Resources, Committee on Educational Programs in Laboratory Animal Science. 1991. Euthanasia. Pp. 67-74 in Education and Training in the Care and Use of Laboratory Animals: A Guide for Developing Institutional Programs. Washington, D.C.: National Academy Press.

NRC (National Research Council), Institute of Laboratory Animal Resources, Committee on Pain and Distress in Laboratory Animals. 1992. Recognition and Alleviation of Pain and Distress in Laboratory Animals. Washington, D.C.: National Academy Press. 137 pp.

Popilskis, S., D. Kohn, J. A. Sanchez, and P. Gorman. 1991. Epidural *vs.* intramuscular oxymorphone analgesia after thoracotomy in dogs. Vet. Surg. 20:462-467.

Roberts, T. D. M. 1954. Cortical activity in electrocuted dogs. Vet. Rec. 66:561-566.

Rubal, B. J., and C. Buchanan. 1986. Supplemental chloralose anesthesia in morphine premedicated dogs. Lab. Anim. Sci. 36:59-64.

Scott, J. P. 1970. Critical periods for the development of social behaviour in dogs. Pp. 21-32 in The Post-Natal Development of Phenotype, S. Kazda and V. H. Denenberg, eds. Prague: Academia.

Sheffy, B. E., J. A. Baker, and J. H. Gillespie. 1961. A disease-free colony of dogs. Proc. Anim. Care Panel 11:208-214.

Short, C. E., ed. 1987. Principles & Practice of Veterinary Anesthesia. Baltimore: Williams & Wilkins. 669 pp.

Skarda, R. T. 1987. Local and regional analgesia. Pp. 91-133 in Principles & Practice of Veterinary Anesthesia, C. E. Short, ed. Baltimore: Williams & Wilkins.

Slattum, M. M., L. Maggio-Price, R. F. DiGiacomo, and R. G. Russell. 1991. Infusion-related sepsis in dogs undergoing acute cardiopulmonary surgery. Lab. Anim. Sci. 41:146-150.

Soma, L. R., ed. 1971. Textbook of Veterinary Anesthesia. Baltimore: Williams & Wilkins. 621 pp.

Soma, L. R. 1987. Assessment of animal pain in experimental animals. Lab. Anim. Sci. 37(Special Issue):71-74.

Soma, L. R., and D. R. Shields. 1964. Neuroleptanalgesia produced by fentanyl and droperidol. J. Am. Vet. Med. Assoc.145:897-902.

Swango, L. J. 1983. Canine Immunization. Pp. 1123-1127 in Current Veterinary Therapy. VIII. Small Animal Practice, R. W. Kirk, ed. Philadelphia: W. B. Saunders.

Thomas, E. D., and J. W. Ferrebee. 1961. Disease-free dogs for medical research. Proc. Anim. Care Panel 11:230-233.

Voith, V. L. 1984. Possible pharmacological approaches to treating behavioural problems in

animals. Pp. 227-234 in Nutrition and Behaviour in Dogs and Cats, R. S. Anderson, ed. Oxford: Pergamon Press.

Wallach, M. B., K. E. Peterson, and R. K. Richards. 1981. Electrophysiologic studies of a combination of secobarbital and dibucaine for euthanasia of dogs. Am. J. Vet. Res. 42:850-853.

Warrington, R. 1974. Electrical stunning, a review of the literature. Vet. Bull. 44:617-628.

Willis, M. B. 1989. Genetics of the Dog. London: H. F. & G Witherby. 417 pp.

6

Special Considerations

PROTOCOL REVIEW

One of the many important responsibilities of an institutional animal care and use committee (IACUC) is to review the protocols of research projects in which dogs will be used (9 CFR 2.31; PHS, 1986). The protocol-review mechanism is designed to ensure that investigators consider the care and use of their animals and that protocols comply with federal, state, and institutional regulations and policies. In addition, the review mechanism enables an IACUC to become an important institutional resource, assisting investigators in all matters involving the use of animals. Although the discussion below is directed to the use of dogs in research, the review requirements apply to all vertebrate species.

Each research protocol must completely (but concisely) delineate the proposed study, including a description of each of the following:

- the purpose of the study;
- the rationale for selecting dogs as the research subjects;
- the breed, age, and sex of the dogs to be used;
- the numbers of dogs in various groups of the protocol and the total number to be used;
- experimental methods and manipulations;
- experimental manipulations that will be performed repeatedly on an individual dog;

- preprocedural and postprocedural care and medications;
- procedures that will be used to minimize discomfort, pain, and distress, including, where appropriate, the use of anesthetics, analgesics, tranquilizers, and comfortable restraining devices;
- the euthanasia method, including the reasons why it was selected and whether it is consistent with the recommendations of the American Veterinary Medical Association Panel on Euthanasia (AVMA, 1993, et seq.);
- the process undertaken to ensure that there are no appropriate in vitro alternatives, that there are no alternative methods that would decrease the number of animals to be used, and that the protocol does not unnecessarily duplicate previous work; and
- the qualifications of the investigators who will perform the procedures outlined.

One approach used by IACUCs is to have a scientifically knowledgeable member thoroughly review the protocol. The reviewer contacts the investigator directly to clarify issues in question. Later, at an IACUC meeting, the reviewer presents and discusses the protocol and relates discussions with the investigator. Changes or clarifications in the protocol that have resulted from the reviewer's discussions with the investigator are submitted to the IACUC in writing. After presentation of the protocol, the reviewer recommends a course of action, which is then voted on by the IACUC. Another kind of protocol review (which is especially effective in small institutions with few grants) is initial review by the entire IACUC; results are generally available to the investigator within a short period.

Several outcomes of protocol review are possible: approval, approval contingent on receipt of additional information (to respond to minor problems with the protocol), deferral and rereview after receipt of additional information (to respond to major problems with the protocol), and withholding of approval. If approval of a protocol is withheld, an investigator should be accorded due process and be given the opportunity to rebut the IACUC's critique in writing, to appear in person at an IACUC meeting to present his or her viewpoint, or both. It is also important that provision be made for expedited review, in which a decision is reached within 24-48 hours. Expedited reviews should be used only for emergency or extenuating circumstances. When a protocol is submitted for expedited review, each member of the IACUC must have an opportunity to review it and may call for a full committee review before approval is given and before animal work begins (McCarthy and Miller, 1990).

The question of protocol review for scientific merit has been handled in a variety of ways by IACUCs. Many protocols are subjected to extensive, external scientific review as part of the funding process; in such instances, the IACUC can be relatively assured of appropriate scientific review. In

the case of studies that will not undergo outside review for scientific merit, many IACUCs require signoff by the investigators, department chairmen, or internal review committees; this makes the signer responsible for providing assurance that the proposed studies have been designed and will be performed "with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society" (NRC, 1985, p. 82; PHS, 1986, p. 27). Occasionally, IACUC members and investigators differ as to the relevance of proposed studies to human and animal health and the advancement of knowledge. Each institution should develop guidelines for dealing with this potential conflict.

RESTRAINT

Some form of restraint is generally necessary to control a dog during a procedure (see guidelines in NRC, 1985, p. 9). The method used should provide the least restraint required to allow the specific procedure to be performed properly, should protect both the dogs and personnel from harm, and should avoid causing distress, physical harm, or unnecessary discomfort. In handling and restraining dogs, it is helpful to understand species-typical behavior patterns and communication systems.

A small or medium-size dog can be picked up by placing one hand under the chest and abdomen while restraining the head with a leash. Lifting a large dog might require two people. It is important to remember that males are sensitive to touch near their genitalia. Minor procedures, such as taking a rectal temperature or administering a subcutaneous injection, can usually be accomplished by one person using minimal restraint. During venipuncture, sufficient restraint should be used to avoid repeated needle insertions and to prevent the development of painful hematomas. Kesel and Neil (1990) detail methods for handling and restraining animals.

If dogs are to be restrained frequently or for long periods or if the restraint method used is especially rigorous, it might be necessary to train them to tolerate the restraint. Training sessions should use positive-reinforcement techniques; negative-reinforcement techniques are not desirable. Physical abuse (9 CFR 2.38f2i) and food or water deprivation (9 CFR 2.38f2ii) must not be used to train, work, or handle dogs, although food and water may be withheld for short periods when specified in an IACUC-approved protocol (9 CFR 2.38f2ii).

SPECIAL CARE FOR ANIMAL MODELS

The remainder of this chapter deals with some common uses of laboratory dogs in which aspects of care vary from the general guidelines provided in previous chapters. It is not intended to present an exhaustive list

of canine models that require special housing and husbandry, but rather to provide the reader with different types of canine models that can serve as examples of how housing and husbandry can be modified to achieve animal well-being. The suggestions offered here are not to be construed as the only ones possible. The committee recognizes that not every research procedure and circumstance can be anticipated, and it assumes that sound professional judgment, good veterinary practices, and adherence to the spirit of this guide will prevail in unusual situations.

The final subsection of this chapter introduces the reader to the technique of somatic cell gene therapy. Many disorders of dogs, like those of humans, are caused by single-gene mutations. Scientists are working to develop techniques to cure these disorders permanently by replacing mutant genes with normal ones. For many reasons (see Chapter 2), the dog is an ideal model for evaluating the safety and efficacy of gene therapy.

Aging

Clinical Features

Life expectancy and disease incidences vary among breeds of dogs; therefore, it is not possible to state a specific age at which dogs become old. Common laboratory dogs, such as beagles, begin some aging changes when they are 8-10 years old. Such physical features as graying of the haircoat, especially around the face, are often apparent as aging begins.

As dogs age, they tend to become less active and to exhibit such signs of mental deterioration as poor recognition of caretakers, excessive sleeping, and changes in personality. Senile plaques, similar to those found in humans with senile dementias, have been reported in the brains of old dogs (Wiśniewski et al., 1970). Various forms of arthritis, spondylosis, and degenerative joint disease are common and contribute to problems in mobility and to the apparent diminution of mental alertness. Older dogs might decrease their daily food intake, become slow eaters, or become irregular in their eating habits. Dental problems—including periodontal disease, tooth abscesses, and oral-nasal fistulas—increase; the importance of these problems is probably underestimated (Tholen and Hoyt, 1983). Dogs more than 6 years old develop lenticular sclerosis, which results in a bluish appearance within the pupil. Visual acuity decreases with age and is often associated with cataracts, secondary glaucoma, and other diseases (Fischer, 1989). There is also apparent hearing loss.

Atrophy of the thyroid gland and an increased number of thyroid tumors have been reported, and signs of hypothyroidism are common (Haley et al., 1989; Milne and Hayes, 1981). Thyroid atrophy and the propensity of older dogs to develop hypothermia might be related (B. A. Muggenburg,

Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute, Albuquerque, N.M., unpublished). A decreased response to antigens and changes in lymphocyte function might indicate that the older dog is less able to resist infectious diseases (Bice and Muggenburg, 1985). Some changes in common blood-cell measures and serum chemistry become important when these are used for diagnosis (Lowseth et al., 1990a). The incidence of neoplasia increases strikingly (MacVean et al., 1978); for example, lung tumors, nearly unknown in young dogs, can reach an incidence as high as 10 percent in dogs over 10 years old (Ogilive et al., 1989). Pulmonary function decreases with age because of reduced lung volumes and decreased elasticity (Mauderly and Hahn, 1982). Chronic renal diseases often occur and require frequent monitoring. Chronic heart disease is also fairly common, and clinical signs can appear suddenly in old dogs.

Husbandry and Veterinary Care

Housing and environment. Accommodation should be made for dogs that have problems moving comfortably on floor grates or through guillotine-like doors in kennel buildings. Because of their decreased mobility and impaired thermoregulatory function, aging dogs with access to outdoor areas should be checked frequently to be certain that they are able to get inside to escape the cold or heat. Automatic watering devices might become difficult to use; for some old dogs, it might be necessary to switch to water pans placed on the floor.

Nutrition. Differentiation between age-related and disease-caused changes in eating habits might be difficult. It is important that animal-care personnel become familiar with and closely monitor daily eating habits of older dogs. Frequent checking and recording of body weights can help in assessing whether food intake is adequate. Changes in diet are sometimes dictated by the clinical diagnosis of disease (e.g., a low-protein diet for chronic, progressive renal disease and a low-sodium diet for chronic heart failure).

Physical characteristics of food can affect dental hygiene. Soft and wet food fed over many years can contribute to dental disease. Feeding dry dog food and providing hard objects for chewing can be helpful in the long-term management of dental problems. Routine dental care, including the removal of calculus and polishing, is essential.

Veterinary care. The extent of chronic disease problems in older dogs requires more intensive veterinary care, extensive diagnostic investigations, and good nursing. Dosages of some medications might have to be reduced, because drugs are commonly metabolized more slowly in old than in young adult dogs. Such drugs as digoxin should be monitored by measuring blood

concentrations to decrease the risk of overdosing (De Rick et al., 1978). A useful reference on geriatric veterinary medicine is *Geriatrics and Gerontology* (Goldston, 1989).

Reproduction

Bitches. Andersen and Simpson (1973) have described reproductive senescence in beagle bitches. Intact bitches exhibit irregular estrous cycles, accompanied by decreased fertility, and prolonged periods of anestrus. The mortality rate is higher among puppies born to older bitches than among puppies born to bitches less than 3 years old.

The most common pathologic condition of the uterus of aged bitches is pyometra (Andersen and Simpson, 1973; Järvinen, 1981; Whitney, 1967). Vaginal fibromuscular polyps are also common (Andersen and Simpson, 1973). The age-specific incidence of mammary gland neoplasms in intact beagle bitches continues to increase throughout life (Taylor et al., 1976).

Dogs. Aging dogs have testicular atrophy and often develop prostatic hypertrophy and hyperplasia and have episodes of prostatitis (Lowseth et al., 1990b). There are also metaplastic changes in the bladder (Lage et al., 1989).

Cardiovascular Diseases

Congenital Heart Defects

Clinical Features

Dogs with hereditary cardiovascular malformations have been used to investigate the role of genetic and embryologic factors in the cause and pathogenesis of congenital heart defects, including hereditary patent ductus arteriosus, conotruncal defects (e.g., ventricular septal defect, tetralogy of Fallot, and persistent truncus arteriosus), discrete subaortic stenosis, and pulmonary valve dysplasia. Congenital heart defects in dogs have been summarized by Buchanan (1992) and Eyster (1992). Table 6.1 describes and lists the clinical signs of selected heart defects. Each of those defects is transmitted as a lesion-specific genetic defect in one or more breeds. A model for each defect has been developed at the University of Pennsylvania School of Veterinary Medicine by selective breeding of affected dogs (Patterson, 1968), as follows: patent ductus arteriosus, toy and miniature poodles (Ackerman et al., 1978; De Reeder et al., 1988; Gittenberger-de Groot et al., 1985; Knight et al., 1973; Patterson et al., 1971); conotruncal defects, keeshonden (Patterson et al., 1974, 1993; Van Mierop et al., 1977); discrete subaortic

TABLE 6.1 Selected Congenital Cardiac Defects in Dogs

Defect	Description	Clinical Signs
Patent ductus arteriosus	Failure of ductus arteriosus to close after birth. If pulmonary vascular resistance is low, blood flows through ductus from left to right. Pulmonary hypertension and left ventricular hypertrophy result unless ductus opening is small. If ductus is large and pulmonary vascular resistance is high, pulmonary arterial pressure can exceed aortic pressure, and blood will flow from right to left, sending venous blood into ascending aorta.	Vary with size of duct and pulmonary vascular resistance from subclinical to heart failure. Early signs include poor growth, coughing, and dyspnea. Aneurysm can occur at site of ductus arteriosus. Polycythemia occurs in cyanotic dogs with a large patent ductus arteriosus (PDA), pulmonary hypertension, and right to left blood flow through the PDA.
Conotruncal defects		
Ventricular septal defect	Failure to complete formation of the conotruncal septum results in ventricular septal defects (VSDs) of varied size, involving the lower and middle portions of the crista supraventricularis (Type I, subarterial VSD). Pups with large VSDs usually die from pulmonary edema in the neonatal period. Smaller VSDs are compatible with long life unless complicated by pulmonary hypertension and congestive heart failure.	Vary with size of defect from subclinical to signs of respiratory and right-side heart failure, including cyanosis, dyspnea, weakness, and anorexia.
Tetralogy of Fallot	Consists of pulmonic stenosis (valvular, infundibular, or both), conal ventricular septal defects, dextroposition of aorta with overriding of ventricular septum, and right ventricular hypertrophy. Some dogs have pulmonary valve atresia (pseudo-truncus arteriosus).	Depend on severity of pulmonic stenosis and ventricular septal defect. Can include decreased body size, fatigue, cyanosis, and secondary polycythemia.
Persistent truncus arteriosus	Severe but rare anomaly. Complete failure of septation of conus and truncus regions, producing large conal ventricular septal defect and single arterial outlet vessel.	Cyanosis and dyspnea. Dogs rarely survive neonatal period.

TABLE 6.1 *Continued*

Defect	Description	Clinical Signs
Discrete subaortic stenosis	Narrowing of left ventricular outflow tract, most commonly by fibrous ring just below aortic semilunar valves, with concomitant obstruction of blood flow, left ventricular hypertrophy, and increased left ventricular pressure.	Vary with degree of stenosis from asymptomatic to poor growth, exercise intolerance, syncope, ventricular arrhythmias, pulmonary edema, and sudden death.
Pulmonary valve dysplasia	Varies from mild thickening of leaflets surrounding narrowed pulmonary orifice to complete fusion of leaflets and doming of valve. Interferes with emptying of right ventricle.	Vary from asymptomatic to dyspnea, fatigability, and right-side heart failure.

stenosis, Newfoundlands (Patterson, 1984; Pyle et al., 1976); and pulmonary valve dysplasia, beagles (Patterson, 1984; Patterson et al., 1981). Conotruncal defects in the keeshond breed are determined by the effect of a single major gene defect (Patterson et al., 1993). Subaortic stenosis in Newfoundlands also appears to be monogenic with variable expression (Patterson, 1984). Patent ductus arteriosus and pulmonary valve dysplasia are inherited in a non-Mendelian pattern.

Husbandry and Veterinary Care

Animals with cardiac defects often require exercise restriction to avoid cyanosis and congestive heart failure. The need for restriction must be decided for each dog on the basis of cardiac status. If the clinical manifestations of severe defects (e.g., respiratory distress, severe cyanosis, and congestive heart failure) cannot be relieved with appropriate surgical methods or cardiovascular drugs (e.g., cardiac glycosides and diuretics), the dog should be humanely killed (see Chapter 5).

Reproduction

Only dogs with mild to moderate cardiac defects or those in which the defects have been surgically corrected should be selected for breeding. Severely affected dogs do not survive to breeding age, or they develop clinical manifestations that preclude their use for reproduction (e.g., marked cyanosis

and congestive heart failure). Methods of modern clinical cardiology—including auscultation, radiography, echocardiography, cardiac catheterization, and angiocardiography—are necessary for accurate diagnosis and evaluation of the severity of defects in candidates for breeding. Therefore, appropriate facilities and equipment and personnel qualified to use such equipment must be available before a breeding colony is established. Once it is established, the health status of breeding stock and their offspring must be carefully monitored.

Induced Heart Defects

Clinical Features

Many animal models of cardiac disease are surgically induced in physiologically normal animals. Aims of the research protocol and humane considerations must often be carefully balanced to ensure that the maximal amount of information is derived from each animal.

Surgically induced models can be broadly divided into models of volume or pressure overload produced by creating valvular or interchamber defects, models of ischemic injury, and models of arrhythmia (Gardner and Johnson, 1988). Long-term management of these models can be difficult because they are frequently on the verge of physiologic decompensation and at risk of sudden death. Table 6.2 lists the signs of cardiac failure.

TABLE 6.2 Clinical Signs of Heart Failure in Dogs

Type of Heart Failure	Clinical Signs
Left-side	Exercise tolerance decreases. Inappropriate dyspnea follows exercise. Pulmonary venous pressure increases, initially causing pulmonary and bronchial congestion and reflexogenic bronchoconstriction. Repetitive coughing follows exercise. Orthopnea, with a reluctance to lie down; restlessness at night; and paroxysmal dyspnea are common. In severe failure, pulmonary edema, severe dyspnea at rest, and rales on auscultation become evident.
Right-side	Systemic venous congestion occurs with engorgement of jugular veins. Liver and spleen are enlarged and often palpable. Fluid retention is usually first manifested as ascites; subcutantous edema, hydrothorax, or hydropericardium can follow. Disturbances of gastrointestinal function, with diarrhea, can occur.
Generalized	Signs of both left- and right-side failure occur.

Husbandry and Veterinary Care

The management of chronic dog models of induced heart failure is most successful if the approach used is interdisciplinary, involving cardiologists, surgeons, and veterinary-care staff. Goals of long-term management include identifying potential complications, selecting therapeutic regimens, and developing long-term monitoring protocols. The following general guidelines should be tailored to the type of disorder induced, the dogs' well-being, and the goals of the research protocol.

Postoperative care. Postoperative care depends on the type of heart disease induced. Medical management should continue after successful recovery from surgery because a specific surgical protocol does not always produce a physiologically consistent model. Some dogs achieve a stable, compensated postoperative condition; others undergoing the same procedure develop signs of acute heart failure immediately after surgery.

Careful monitoring on the days after surgery is critical. Meticulous physical examinations should be performed on physiologically stable dogs at least once a day until they have recovered from surgery. Physiologically unstable dogs should be examined more often. Vital signs should be monitored, and particular attention should be given to physical findings related to the cardiovascular system. Mucous membrane color, capillary-refill time, and temperature of extremities can be abnormal if peripheral perfusion is seriously impaired. The pulse quality of the femoral artery can be used to assess systemic perfusion. Auscultation should be used to detect abnormal cardiac sounds, and electrocardiography should be performed to diagnose arrhythmias. Assessment of respiratory rate and depth should be combined with careful auscultation of all lung fields to detect early signs of pulmonary complications. Echocardiography, if available, can be used to evaluate cardiac function and contractility.

Good nursing care is important. Special diets, such as canned dog food or dry food mixed with chicken broth, can be offered to encourage food intake. Ideally, dogs should be housed in a dedicated recovery room and returned to the regular housing area only when they are physiologically stable and have recovered fully from surgery. Decreased exercise tolerance secondary to diminished cardiac reserve might affect the extent of activity that a dog can withstand.

Complications. Potential complications associated with surgical and catheterization procedures should be anticipated, including infection of the operative site, bacteremia, and endocarditis. Dogs at high risk for complications are the ones that undergo serial catheterization procedures and those with bioimplants, such as prosthetic valves and pacemakers (Dougherty,

1986). Baseline monitoring should include scheduled physical examinations and complete blood counts (CBCs). A blood culture should be submitted to the laboratory for any animal with a persistent fever or an intermittently increased temperature. If infection is suspected, a broad-spectrum antibiotic, such as one of the cephalosporins, should be administered pending receipt of culture and sensitivity results.

Banding of the great vessels with various materials is a standard procedure for producing volume- and pressure-overload models of ventricular hypertrophy, coarctation of the aorta, and obstruction of right ventricular outflow. Vessel erosion caused by the material used (Gardner and Johnson, 1988) and hemorrhage secondary to banding procedures are common complications that should be included in the differential diagnosis of any banded animal that suffers an acute onset of lethargy, paleness of the mucous membranes, or dyspnea. Those are also clinical signs of heart failure, so it is important to perform auscultation of the chest and suitable diagnostic tests, such as radiography or thoracentesis, to make an accurate diagnosis. A dog that is hemorrhaging should be euthanatized.

Surgical procedures used to induce cardiac disease invariably cause disruption of the endothelium and put the dogs at risk for thrombosis and embolism. Dogs undergoing cardiac catheterization or surgery of the cardiac valves are at greatest risk. Clinical signs reflect the organs involved.

Long-term monitoring. In a study of extended duration, assessment of each dog's general health and cardiovascular system should be continuous. The type and frequency of examinations will depend on whether the model is physiologically stable or unstable. For example, a dog with induced mitral regurgitation, which is defined as a 50 percent reduction in forward stroke volume and a pulmonary capillary wedge pressure of 20 mm Hg, can develop life-threatening pulmonary edema (Nakano et al., 1991; Swindle et al., 1991). Frequent monitoring and auscultation are required to detect early signs of respiratory compromise so that the dog will not die before therapy can be initiated or the dog can be studied. Similarly, a dog with induced right ventricular pressure overload requires frequent monitoring because decreased coronary blood flow can lead to acute right-side heart failure (Fixler et al., 1973; Vlahakes et al., 1981). Conversely, a stable model of left ventricular hypertrophy can be produced in 8-week-old pups by aortic banding, which causes a systolic pressure gradient of 15-20 mm Hg (O'Kane et al., 1973). Dogs with induced tricuspid valve insufficiency can tolerate increased venous pressure and a slight reduction in cardiac output for years, although some develop ascites and reduced serum albumin (Arbulu et al., 1975). These models require less frequent monitoring.

Equipment. Follow-up care and monitoring require appropriate equip-

ment and laboratory support for obtaining CBCs, blood cultures, serum chemistry profiles, and blood-gas analyses. Electrocardiography and echocardiography should be available for assessing cardiac rhythm and function, respectively. Echocardiography is also a useful noninvasive method for monitoring changes in cardiac wall thickness, cardiac motion, and chamber size as cardiac disease progresses. A cardiac catheterization laboratory should be available for performing hemodynamic and angiographic studies.

Pharmacologic therapy. Pharmacologic management of dogs that develop complications or clinical signs of heart failure must be coordinated between the veterinary unit and the investigator to prevent the administration of medications that could compromise the scientific aims of the study. Diuretics can be used to treat pulmonary edema and reduce plasma volume, but their effects on serum electrolytes and the reduction of venous return and cardiac output should be considered. Vasodilators, calcium antagonists, β-blocking drugs, and positive inotropic agents should be available for managing acute clinical events; however, long-term use of these drugs is usually contraindicated because of their effects on the disease process being studied (Bonagura, 1986; Swindle et al., 1991).

Hypertension

Clinical Features

To provide proper care for hypertensive dogs and to avoid inappropriate treatment that can be detrimental to the dogs and compromise the study, it is necessary to have a full understanding of the pathophysiology of hypertension and of the specific method that is used to induce it. Generally, hypertension in dogs is induced by constricting the renal artery. The resulting reduction in renal perfusion causes systemic arterial pressure—and renal arterial pressure distal to the constriction—to rise enough to maintain renal function. A discussion of the relationship between renal function and the long-term control of blood pressure can be found in any standard physiology textbook (e.g., Guyton, 1991).

Two methods are most commonly used to induce renal vascular hypertension: partial constriction of one renal artery (the 2-kidney, 1-clip method) and unilateral nephrectomy and partial constriction of the remaining renal artery (the 1-kidney, 1-clip method). Both those methods produce what is called Goldblatt hypertension, but the mechanisms responsible for the hypertension are different. The 2-kidney, 1-clip model depends more heavily on the renin-angiotensin system than the 1-kidney, 1-clip model and responds to acute treatment with angiotensin-converting enzyme (ACE) inhibitors, which block the conversion of angiotensin I to angiotensin II. The

1-kidney, 1-clip model requires chronic treatment with ACE inhibitors to lower blood pressure. The reason for that difference is described in detail by Guyton (1991).

The greatest success in producing hypertension while reducing the incidence of malignant hypertension and renal failure is achieved by reducing renal arterial flow by exactly 50 percent. Renal blood flow is usually measured when the arterial clamp (Goldblatt clamp) is adjusted during surgery; this obviates later surgery to readjust the degree of constriction. Methods have been developed for measuring renal blood flow chronically and adjusting the renal artery clamp (Ferrario et al., 1971), and more recently a technique has been described for producing hypertension reliably by gradually constricting the renal artery with constrictors fabricated of ameroid, a hydroscopic material made of compressed casein cured in formalin (Ben et al., 1984; Brooks and Fredrickson, 1992).

Other methods that have been used for inducing hypertension include a 2-kidney, 2-clip model in which Goldblatt clamps or ameroid constrictors are applied to both renal arteries; wrapping of one or both kidneys with silk or cellophane; a combination of unilateral nephrectomy and wrapping of one kidney; and placing sutures in a figure 8 configuration on the surface of one or both kidneys (the Grollman model). The creation of hypertension with deoxycorticosterone acetate (DOCA) and common salt has not been as successful in dogs as it has in rats, because dogs are reluctant to eat a high-salt diet or drink a saline solution. However, moderate hypertension in dogs can be achieved with DOCA administration alone. A colony of spontaneously hypertensive dogs has been described (Bovée et al., 1986).

Husbandry and Veterinary Care

Proper care of hypertensive dogs involves the following:

- careful design and establishment of the hypertensive model to produce stable hypertension;
- routine evaluation of renal function;
- regular and frequent monitoring of blood pressure;
- regular monitoring of the retinas;
- appropriate treatment with antihypertensives when required; and
- careful husbandry.

Evaluation of renal function. Routine evaluation of renal function is essential because renal failure is a common complication in dogs with experimental hypertension. Renal failure can be caused by too much constriction of the renal artery, a rapid increase in both systolic and diastolic pressures (malignant hypertension), or the inappropriate use of antihypertensives.

Evaluation of renal function is especially important with use of the 1-kidney, 1-clip and 2-kidney, 2-clip models (which cause the most severe hypertension) and during antihypertensive therapy. In hypertensive dogs, renal function is compromised to such an extent that blood pressure must be raised to maintain sodium balance. If antihypertensive therapy lowers blood pressure too much, acute renal failure will ensue.

The most reliable and easily measured indicators of renal function are serum creatinine concentration and blood urea nitrogen (BUN). Although they depend somewhat on the type of assay, normal serum creatinine for the dog ranges between 0.4 and 1.3 mg/dL and BUN between 10 and 25 mg/dL. Serum creatinine and BUN should be determined in each dog before hypertension is induced to avoid using dogs with already-compromised renal function. In Goldblatt hypertensive models, serum creatinine should be determined daily for the first 5 days after surgery and twice a week thereafter. If ameroid constrictors are used, daily evaluations should continue through the second week after surgery because it takes 4-5 days for ameroid constrictors to reach maximal constriction. In models in which hypertension is not as severe, such as the 2-kidney, 1-clip and 1-kidney, 1-wrapped hypertensive models, renal function is less likely to be impaired, and serum creatinine concentration and BUN might not be increased, but they should be evaluated at least once during the 10-day postoperative period.

If renal-function tests show signs of renal failure, corrective action should be taken. Too-severe constriction of the renal artery can be corrected surgically, or the study can be terminated by euthanatizing the animal. Renal failure caused by lowering blood pressure to below the renal autoregulatory range should be corrected by reducing the dose of the antihypertensive drug to a point that allows blood pressure to remain high enough to maintain renal function. Malignant hypertension can be treated with antihypertensives and reduced salt intake (Ross, 1989; see below).

Measurement of arterial blood pressure. Blood pressure should be determined routinely after surgery. It can be done with indirect methods, such as placing a pressure cuff at the base of the tail (Petersen et al., 1988) or above the hock, or with direct methods, such as chronic implantation of arterial catheters or acute femoral arterial catheterization. To avoid complications associated with exteriorized catheters, some investigators now use methods that do not require exteriorized components, such as a Vascular Access Port (Access Technologies, Skokie, Ill.) (Mann et al., 1987), or chronic instrumentation, such as constriction of the carotid loop (Brooks et al., 1991). In addition, improved telemetric monitoring (Lange et al., 1991) has the potential to allow continuous monitoring of blood pressure over a number of days or weeks.

It is important to establish a baseline blood pressure before inducing

hypertension. Measuring blood pressure several times permits the dog to become accustomed to the monitoring technique and thereby avoids increases in blood pressure caused by stress. Some investigators measure blood pressure indirectly (e.g., with the tailcuff method) before surgery and use more direct methods later. That is done in recognition that indirect methods can lead to a deviation of up to 10 mm Hg from true arterial pressure. Normal systolic blood pressure ranges from 112 to 142 mm Hg; normal diastolic pressure from 56 to 110 mg Hg. Measurements greater than 160/95 indicate hypertension.

Treatment for hypertension. When induced correctly, surgically created hypertension is sustained and has few complications. If necessary, hypertensive dogs can be maintained on special diets (see below) and given diuretics or other antihypertensive drugs when needed. Some drugs readily available for treatment of hypertensive dogs are listed in Table 6.3.

Malignant hypertension must be diagnosed quickly and treated aggressively. The most striking clinical sign of malignant hypertension can be blindness caused by retinal detachment, which is usually preceded by retinal hemorrhage, dilation of retinal vessels, and subretinal edema. The dogs do not appear to be in pain but often bump into walls and might become disoriented or sit quietly in their pens or cages. Diagnosis can easily be confirmed with an ophthalmologic examination. If blood pressure can be controlled and retinal disinsertion (detachment from the ora ciliaris retinae)

TABLE 6.3 Drugs Available for the Oral Treatment of Hypertension in Dogs[a]

Generic Name	Dosage, mg/kg	Frequency of Administration	Class
Chlorothiazide	20-40	Every 12 hr or daily	Diuretic
Hydrochlorothiazide	2-4	Every 12 hr or daily	Diuretic
Furosemide[b]	2-4	Every 8-12 hr	Diuretic
Propranolol	0.25-0.5	Every 8 hr	β-Adrenergic antagonist
Hydralazine	1-3	Every 12 hr	Vasodilator
Prazosin	0.25-2	Every 8 hr	Vasodilator
Verapamil[c]	1-2	Every 8 hr	Vasodilator; calcium-channel blocker
Captopril	0.5-1	Every 8-12 hr	Angiotensin-converting enzyme inhibitor

[a]Adapted from Ross, 1989; printed with permission of the author and W. B. Saunders, Philadelphia, Pennsylvania.

[b]Can also be given intramuscularly or intravenously at 2-4 mg/kg.

[c]Can also be given intravenously at 0.05-0.15 mg/kg.

does not occur, some vision might be restored in 2-3 weeks. Malignant hypertension often responds well to treatment with ACE inhibitors. Diuretics can also be administered if care is taken to avoid a precipitous drop in renal blood flow. Vasodilators can be used with caution. If the cause of the malignant hypertension is overconstriction of the renal artery, ACE inhibitors can be used to stabilize the dog while the stricture is surgically corrected.

Husbandry. Routine care of hypertensive dogs must include a consideration of diet because both salt intake and protein intake will affect blood pressure and renal function. A high salt intake will exacerbate hypertension, and a high protein intake might accelerate the loss of renal function. To avoid unintended changes in diet that could compromise their dogs and studies, investigators, veterinarians, and others caring for hypertensive dogs should establish dietary requirements before beginning studies.

For dogs with hypertension and renal failure, the diet should contain 0.1-0.3 percent sodium on a dry-weight basis or 10-40 mg/kg per day (5-20 mg/lb per day) (Ross, 1989). Low-protein diets (less than 15 percent) that are also low in sodium (e.g., K/D, Hill's Pet Products, Inc., Topeka, Kansas) are available and should be fed in adequate amounts—generally 1 can or 2 cups of dry food for each 10 kg (20 lb) of presurgical body weight. The protein content of some commercially available diets might be too low to maintain ideal body weight, but diets that combine a higher protein content with a lower sodium content are available (e.g., R/D, Hill's Pet Products, Inc., Topeka, Kansas). As in any dog model, following the body weight of an animal regularly is a good way to monitor the animal's overall health.

There is usually no reason to restrict primary enclosure size for hypertensive dogs. Whether they should be exempted from an exercise program depends on their postoperative course. If the hypertensive condition stabilizes and there are no complications, exemption from exercise should not be necessary. Blood pressure is known to increase in stressful conditions; therefore, it is important that such conditions be avoided (e.g., dogs that are housed or exercised in pairs or groups should be monitored to ensure that they are compatible).

Ehlers-Danlos Syndrome

Clinical Features

Ehlers-Danlos syndrome type 1 is an autosomal dominant condition of humans for which there are analogues in dogs and other mammals (Hegreberg et al., 1969, 1970). The disease is caused by a defect in metabolism of

dermal collagen that results in a skin tensile strength less than 10 percent of normal. Fibrous tissue and bone are subclinically affected in some cases (Minor et al., 1987). Multiple lacerations are often observed. The hyperextensible skin can cause superior entropion, inferior ectropion, or both.

Husbandry and Veterinary Care

The extreme fragility of the skin must be considered in managing dogs with this syndrome. Affected dogs should be housed singly in smooth-surfaced pens of glass, concrete, or sheet steel. Automatic watering valves and other projections should be avoided. The dogs' nails should be kept trimmed. Some dogs might have to wear Elizabethan collars for extended periods to prevent self-inflicted wounds. Dogs should be given opportunities for exercise, either singly or in small groups, by being released under supervision into an exercise pen or room that is free of sharp projections. Leash-walking should be avoided.

Wound management is relatively simple. Wounds tend to heal well, possibly because hyperextensible skin places little tension on wounds. Cutting suture needles and single-stranded nylon suture material can tear through the skin, but tapered needles and braided sutures, such as those of polygalactin 910 (Vicryl), are well tolerated. It is important to avoid placing too much tension along a single suture line. Hygromas and hematomas, which can become large under loose skin, can be encountered, either as sequelae to lacerations or as primary events. Adhesive tape should never be applied directly to the skin or fur during bandaging because it can tear the skin when the bandage is removed. Entropion and ectropion can be corrected surgically; however, repeated correction might be necessary.

Reproduction

All affected dogs appear to be heterozygotes; affected homozygotes probably die in utero. To increase fertility, to avoid injury of affected animals, and to prevent conception of homozygotes, it is preferable to select normal bitches and affected males for breeding and to use artificial insemination. Heterozygous affected pups can be identified at birth by the fragility and hyperextensibility of their skin, as can heterozygous fetuses in late gestation.

Endocrinologic Diseases

Clinical Features

Endocrinopathies in the dog pose diagnostic and therapeutic challenges because they are complicated physiologic derangements that often involve multiple organ systems. An endocrinopathy might be a desired element of an experimental design or simply a spontaneous random occurrence that would be expected in any canine population. Table 6.4 lists the major endocrinopathies that have been documented in dogs. Discussions in this section are limited to endocrinopathies that either are induced in experimental animals or are undesired results of management procedures or investigational protocols. Hypothyroidism and hyperadrenocorticism (Cushing's disease), two major endocrinopathies often seen in clinical veterinary practice, are not discussed here but are well described in the veterinary medical literature (e.g., Capen and Martin, 1989; Chester, 1987, Drazner, 1987a; Feldman, 1989; Hsu and Crump, 1989; Peterson and Ferguson, 1989). A brief review of disorders of calcium metabolism is included because hypocalcemia caused by iatrogenic hypoparathyroidism occasionally occurs in a research setting, and hypercalcemia is often mistakenly attributed to parathyroid dysfunction.

TABLE 6.4 Selected Endocrine Disorders in Dogs

Affected Organ	Diseases
Adrenal cortex	Hyperadrenocorticism Hypoadrenocorticism
Adrenal medulla	Pheochromocytoma
Pancreas	Diabetes mellitus Gastrinoma
Parathyroid	Hyperparathyroidism Hypoparathyroidism
Pituitary	Acromegaly Diabetes insipidus Hypopituitarism
Thyroid	Hyperthyroidism Hypothyroidism
Multiple glands	Hyperlipidemia Hypoglycemia

TABLE 6.5 Common Clinical Signs of Selected Canine Endocrinopathies

Endocrinopathy	Common Clinical Signs
Diabetes mellitus	Hyperglycemia, polydipsia, polyuria, glycosuria, increased food consumption but loss of weight, bilateral cataract development, weakness
Hypoadrenocorticism	Weakness, vomiting, diarrhea, bradycardia, acute collapse
Acromegaly	Respiratory stridor, increased interdental spaces, prominent skin folds, abdominal enlargement, fatigue
Hypercalcemia	Mental dullness; muscular weakness; tachycardia; upper gastrointestinal signs, including anorexia, nausea, and vomiting; signs of renal disease, including nephrocalcinosis, renal calculi, and secondary renal failure
Hypocalcemia	Muscle tremors, tetany, seizures

Common clinical signs of the endocrinopathies to be discussed are listed in Table 6.5. They range from very subtle changes to acute crises. Most are nonspecific and can also be seen in various nonendocrine disorders. Detailed discussions of endocrinopathies can be found in the veterinary medical literature (e.g., Drazner, 1987b; Ettinger, 1989; Feldman and Nelson, 1987; McDonald and Pineda, 1989; Morgan, 1992).

Husbandry and Veterinary Care

Procedures for managing dogs with endocrinopathies are dictated by both the experimental design and the animals' welfare.

Diabetes mellitus. Diabetes mellitus in the dog is a recognized spontaneously occurring model (Kramer, 1981), and the disease is readily induced either by chemical ablation of the pancreatic β-cells or by total pancreatectomy (Mordes and Rossini, 1985). Frequent monitoring is mandatory for the successful management of dogs with diabetes mellitus. Daily measurements, before the first meal of the day and 6-12 hours later, are required to stabilize and control blood glucose in diabetic dogs. The second glucose measurement can be eliminated only when the afternoon blood glucose of an individual dog is consistent from day to day and the insulin requirement for that dog is well established. Blood glucose monitoring should begin after initial administration of diabetogenic chemicals or during the first 24 hours after pancreatectomy. Fasting blood glucose, as measured by the plasma or serum glucose oxidase method, ranges from 65-118 mg/dL (3.6-6.5 mmol/L) in normal adult dogs (Kaneko, 1989).

A number of insulin preparations can be used either singly or in combination in dogs: regular, NPH, lente, and ultralente. Unit doses and prepara-

tion types must be determined for and adjusted to the response of each dog. Insulin should be started at a dose of 1 U/kg per day injected subcutaneously at the time of feeding the first meal of the day. Daily proportions of each preparation included in a therapeutic regimen are determined by trial and error as guided by the results of serial blood glucose measurements. Detailed information on dosage and characteristics of various insulin preparations is available (Nelson, 1989; Schaer, 1992).

In addition to insulin administration, stresses from environmental and experimental manipulation, exercise, concurrent disease, estrus, and changes in food and water intake can cause profound fluctuations in blood glucose concentrations. Blood glucose can be manipulated by adjusting insulin types and dosages. As a general rule, it is preferable to have a slightly hyperglycemic dog rather than a hypoglycemic one because of the potentially disastrous results of a hypoglycemic crisis. If such a crisis occurs, it should be treated with intravenous dextrose and supportive care (Kirk and Bistner, 1985). Supplemental glucose can be given orally if the dog is able to swallow. Obviously, a necessary follow-up includes reviewing and adjusting the insulin dosage and the ratio of short- to long-acting insulin preparations given.

The amount of food fed to each diabetic dog should be standardized at what is necessary to maintain its optimal body weight. The same amount should be fed each day. Once an eating pattern (amount of food eaten and time required for meal consumption) is established for a given dog, its appetite can be used as an indicator of general well-being.

In pancreatectomized dogs, it is necessary to compensate for lost pancreatic exocrine function. That can be accomplished by adding a commercially available digestive enzyme to the food. Some dogs find the product unpalatable, but it is generally accepted if it is mixed with canned food.

Diabetic dogs can be maintained for long periods, but sequelae of diabetes mellitus—including neuropathy, immune system compromise, and delayed healing—do occur, and a shorter than normal life span should be expected.

Hypoadrenocorticism. The canine model of hypoadrenocorticism (Addison's disease) is a classic model in biomedical research (Brown-Sequard, 1856). Hypoadrenocorticism can be induced in dogs by administering the drug mitotane,[1] which chemically ablates the adrenal cortex (Nelson and Woodard, 1949). During induction, a presumptive diagnosis can be made by monitoring changes in serum electrolytes, specifically sodium and potassium. The normal ranges of sodium and potassium concentrations in dog serum are

[1] Chemical name, 1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl) ethane; trivial name, *o,p'*-DDD; brand name, Lysodren.

140-155 mEq/L and 3.7-5.8 mEq/L, respectively (Carlson, 1989). In dogs with hypoadrenocorticism, the sodium-to-potassium ratio is decreased to less than 27:1 (Schrader, 1988), although this hyperkalemia is not pathognomonic. The adrenal corticotropic hormone stimulation test is required for definitive diagnosis (Nichols and Peterson, 1992). In a crisis, resuscitation requires recognizing the problem, intravenously administering 0.9 percent saline solution, replacing glucocorticoids and mineralocorticoids, and possibly providing therapy for hyperkalemia. Long-term maintenance entails glucocorticoid (cortisone) administration, mineralocorticoid supplementation with 9-fluorohydrocortisone acetate,[2] and the addition of sodium chloride to the diet. Electrolytes should be monitored at least weekly once stabilization is achieved. Environmental and experimental stresses and alterations in water and food availability can have substantial effects on electrolyte balance and homeostasis. Additional glucocorticoid (increased by a factor of 2-10) should be administered during periods of stress.

Acromegaly. Acromegaly can be iatrogenically induced in bitches when progesterone is given to prevent estrous cycling (Eigenmann, 1985, 1989). It can also be secondary to increased production of progesterone during diestrus. Progesterone induces acromegaly by increasing the production of growth hormone in the anterior pituitary gland. The excessive release of growth hormone can also induce a "pituitary diabetes" that can be difficult to control with insulin. Cessation of progesterone administration or spaying will reverse acromegalic changes.

Calcium derangements. Although disorders of the parathyroid glands are usually suspected when hypercalcemia or hypocalcemia is present, the calcium abnormality is more often associated with other conditions, including pseudohyperparathyroidism, the most common cause of hypercalcemia (Feldman and Nelson, 1987); hypoadrenocorticism; renal failure; bone lesions; and hypervitaminosis D. Primary hyperparathyroidism in the dog is rare. Pseudohyperparathyroidism (hypercalcemia of malignancy) is a paraneoplastic syndrome that has been recognized in dogs with lymphosarcoma, adenocarcinoma of the anal apocrine glands, multiple myeloma, osteosarcoma, and other neoplasms (Meuten et al., 1982, 1986). Signs of hypercalcemia are not always overt, and treatment should be directed toward the underlying cause.

Causes of hypocalcemia include calcium imbalance during lactation, renal disease, acute pancreatitis, intestinal malabsorption, hypoalbuminemia, and primary hypoparathyroidism (idiopathic or iatrogenic). Iatrogenic

[2] Brand name, Florinef.

hypoparathyroidism is associated with inadvertent damage or removal of the parathyroid glands and is an important consideration in research settings. Surgery involving the ventral neck area or the laryngeal-tracheal area or removal of the thyroid glands carries an increased risk of complications related to parathyroid function. Treatment includes calcium replacement and appropriate management of the precipitating disorder.

Hematologic Disorders

Clinical Features

Canine models of human hematologic disorders have been reviewed (Dodds, 1988, 1989, 1992; Hall and Giger, 1992; Harvey, 1989; Kaneko, 1987; Knoll, 1992). Clinical signs of some of these disorders are listed in Table 6.6.

TABLE 6.6 Inheritance and Signs of Selected Hematologic Disorders in Dogs

Disorder	Inheritance	Clinical signs
Hemophilia A	X-linked	Low factor VIII coagulant activity but normal or increased von Willebrand factor antigen concentrations; spontaneous bleeding diathesis of varied severity, depending on factor VIII activity; severely affected dogs often exhibit spontaneous hemarthroses and large joints. The most common severe inherited bleeding disease. Recognized in most purebreds and in mongrels.
Hemophilia B (Christmas disease)	X-linked	Deficiency of factor IX activity; signs similar to those of hemophilia A. Recognized in 17 breeds.
von Willebrand's disease type I	Autosomal incompletely dominant	Variable deficiency of von Willebrand factor; factor VIII activity might be reduced; and prolonged bleeding time; moderately severe bleeding diathesis of mucosal surfaces. Signs are exacerbated by stress, hypothyroidism, intercurrent disease, trauma, and surgery. Recognized in more than 50 breeds.

continued on next page

TABLE 6.6 Continued

Disorder	Inheritance	Clinical signs
von Willebrand's disease type III	Autosomal recessive	Severe deficiency of von Willebrand factor; factor VIII activity is usually low; indefinitely prolonged bleeding time; mucosal surface bleeding diathesis, which can be severe and is exacerbated by stress, hypothyroidism, trauma, surgery, and intercurrent disease. Recognized in Chesapeake Bay retrievers, Scottish terriers, and Shetland sheepdogs.
Factor X deficiency	Autosomal incompletely dominant	Homozygotes are stillborn or die shortly after birth; affected pups might live for up to 2 weeks and then die of massive internal bleeding; young adults can also exhibit life-threatening hemorrhage, but signs in mature adults are usually mild and confined to mucosal surfaces. Found only in one large family of cocker spaniels.
Thrombopathia	Autosomal	Affected dogs can have no clinical signs or show increased bleeding tendency that can be exacerbated by trauma or surgery. Found in basset hounds and otterhounds.
Cyclic hematopoiesis	Autosomal recessive	Regularly occurring interruptions of bone marrow hematopoiesis with loss of neutrophils from peripheral blood; during these periods, dogs exhibit fever, enteritis, keratitis, pneumonia, and skin infections; infections can become life-threatening if not treated. Found in gray collies.
Pyruvate kinase deficiency	Autosomal recessive	Affected dogs exhibit severe anemia with reticulocytosis, macrocytosis, and polychromasia; hyperbilirubinemia; splenomegaly with extramedullary hematopoiesis; and decreased red cell survival. Found in basenjis, beagles, and cairn terriers.
Erythrocyte phosphofructokinase deficiency	Autosomal recessive	Persistent compensated hemolytic anemia with episodes of intravascular hemolysis, hemoglobinuria, and fever associated with stress or exercise; hemolytic crises follow hyperventilation-induced alkalemia; red cells of affected dogs are extremely alkaline and fragile in vitro. Found in English springer spaniels.

Husbandry and Veterinary Care

Bleeding disorders. Dogs with congenital and acquired bleeding disorders require special housing to minimize the risk of spontaneous or injury-induced bleeding. This is important not only for the animals' welfare, but also for experimental reasons. The basal state of animals that experience repetitive bleeding can be altered by the physiologic stress that such bleeding causes and, if bleeding is severe enough to require transfusions, by repeated exposure to homologous plasma proteins and blood cells. That is of particular concern for dogs with severe disorders, such as hemophilia.

Dogs with bleeding disorders should be housed in enclosures that have smooth sides and fronts with smooth vertical or cross-hatched bars. It is not advisable to use materials that can be climbed (e.g., chain-link fencing) because dogs with bleeding disorders can suffer foot injuries caused by weight-bearing pressure between the toes. Enclosure size is also important. To prevent injury, affected animals should have sufficient space to move about freely but not enough to permit vigorous exercise if they become excited. Enclosures should be square or oblong; injury is more likely to occur in a long, narrow run, especially in dogs with long tails, which during wagging can be traumatized by hitting against the sides. Experience has shown that for dogs weighing from 13.6-36.3 kg (30-80 lb), primary housing measuring about 4 × 6 ft (1.22 × 1.83 m) or 5 × 5 ft (1.52 × 1.52 m) minimizes the risk of injury.

Severely affected dogs should be housed individually because the risk of injury in playing with other dogs is substantial. To provide socialization, it is advisable to construct pens that allow visual contact between dogs; this can be achieved by building pens across an aisle from or perpendicular to each other. Partitions between the runs should be solid for the first 4 ft (1.22 m) in height to prevent injury caused by dogs in adjacent pens playing or fighting through the partition, and the seam with the floor should be smooth.

To avoid foot-pad abrasions, nonslip flooring should not be too rough. A poured rubberized flooring with a small amount of sand added to the last coat should create enough friction to prevent sliding. Nontoxic bedding (e.g., shredded newspaper or shavings) can be used to minimize injuries if sliding does occur. English rubber coits or tennis balls can be used to provide environmental enrichment.

Special arrangements are required for feeding and watering. Automatic watering devices are generally not recommended because the spigots can cause mouth injuries, and bleeding from such injuries is usually difficult to control. It is better to use large water buckets anchored to the sides or fronts of the pens. Dry food should be softened before feeding and supple-

mented with good-quality canned or cooked meat. A hematinic can be added to the food for conditioning. Hard biscuits should not be fed.

Bleeding from small surface injuries to the gums or nose or from toenails that are cut too short can be stopped by using sealant materials, such as Nexaband glue (Tri-Point Medical, LP, Raleigh, N.C.). Bleeding toenails can also be packed with styptic powder, and the soft rubber end cap from an intravenous set or catheter can be wedged tightly over the nail. If necessary, the foot can be bandaged; this supplies enough local pressure to control the bleeding. For animals that experience severe bleeding episodes, transfusion is the treatment of choice. Fresh-frozen plasma, plasma concentrates, platelet concentrates, or packed red cells should be given as required for the specific disorder. Details of management and treatment are summarized elsewhere (Dodds, 1989, 1992).

Another management procedure to keep animals healthy and reduce bleeding risk is prophylactic dentistry, which must be performed very carefully to avoid injury to the gums. Booster vaccinations should not be given during bleeding episodes because they create a transient platelet deficit (Dodds, 1992). In addition, dogs are at increased risk for bleeding episodes for 10-14 days after vaccinations. Affected females sometimes bleed excessively both during estrus and during the 30-40 days beforehand when estrogen concentrations are elevated.

Cyclic hematopoiesis. Colonies of grey collies with cyclic hematopoiesis (formerly called cyclic neutropenia) have special requirements because they are susceptible to recurring infections and anemia (Knoll, 1992). They have a cyclic, profound drop in all their blood-cell classes, although the numbers of each cell type rise and fall at different times. Affected animals rarely live beyond the age of 3 years and experience frequent bleeding episodes from cyclic thrombocytopenia. Respiratory tract and enteric infections are the most debilitating.

Affected animals can often be housed together, but they need scrupulously clean facilities to minimize infection, close clinical monitoring, and supportive therapy. They should be monitored for neutropenia, and prophylactic antibiotics should be administered as neutrophil counts begin to decline.

Other hematologic disorders. Dogs with various other inherited and acquired hematologic diseases also require special care. For example, basenjis with pyruvate kinase deficiency and recurring anemia must be closely monitored because of their increased susceptibility to infection or stress (Hall and Giger, 1992; Harvey, 1989); beagles with hereditary nonspherocytic hemolytic anemia must be closely monitored for episodes of hemolytic crisis (Maggio-Price et al., 1988); and English springer spaniels with erythrocyte phospho-

fructokinase deficiency require special care during episodes of hemoglobinuria or myoglobinuria (Hall and Giger, 1992; Harvey, 1989).

Reproduction

For dogs with severe inherited bleeding disorders—such as hemophilia, von Willebrand's disease, factor X deficiency, and platelet dysfunction (thrombopathia)—special care is needed for breeding, whelping, and rearing of the offspring. Immediately after birth, each pup should be carefully examined for signs of bleeding, its umbilical cord should be ligated, and the potential for trauma from the dam should be minimized. It might be necessary to tranquilize first-time dams slightly to protect the young. When the pups are weaned and start to become more active, blood samples should be taken to determine which pups are affected. In hemophilia, the affected pups from a carrier (heterozygous) dam will be males, unless the sire is a hemophiliac (hemizygote), in which case both affected hemizygote males and homozygote females can be produced. Generally, male pups should be watched more closely, and the affected ones should be removed and housed separately if the litter is too rambunctious. Cages should be relatively small; a floor area of about 30×36 in (76×91 cm) is recommended for the average hemophilic pup.

Affected pups should be watched carefully after vaccinations. Modified live-virus vaccines might induce a relative thrombocytopenia and platelet dysfunction during the period of viremia (i.e., 3-10 days after vaccination) (Dodds, 1992). The pups are at substantial risk for spontaneous or traumatic bleeding at this time because the vaccine effect on platelet function superimposes another hemostatic burden. All vaccinations should be given subcutaneously with a small-gauge needle, preferably 23 or 25 gauge, in the loose skin folds of the neck. Intramuscular injections in affected animals should be avoided.

Affected pups should be housed initially in cages and eventually in small pens. At teething, affected puppies often bleed excessively from the gums; this necessitates use of a topically applied sealant and, on occasion, transfusion therapy.

Immunologic Diseases

Primary Immunodeficiency and Autoimmune Diseases

Clinical Features

Immunodeficiency is characterized by failure to manifest a normal immune response when challenged by infectious agents or other substances

that are foreign to the body. The subnormal response can result from a defect in the afferent, central, or efferent limb of the immune system (see review in NRC, 1989). Immunodeficiency disorders can be primary (i.e., inherited) or secondary (i.e., acquired). Primary immune deficiency can result from an inherited defect in immunocompetent cells or effector mechanisms (e.g., complement or phagocytes) or can be associated with autoimmune disease or a deficiency in growth factors necessary for the optimal function of immunocompetent cells (WHO Scientific Group, 1986). Secondary immune deficiency can be caused by various environmental factors, including x rays, viral agents, toxic chemicals, and dietary deficiencies.

Several primary immunodeficiency diseases have been described in dogs, including selective IgA deficiency (Campbell, 1991; Felsburg et al., 1985; Moroff et al., 1986), IgM deficiency (Mill and Campbell, 1992; Plechner, 1979), common variable immunodeficiency (A. Rivas, New York State College of Veterinary Medicine, Cornell University, Ithaca, N.Y., unpublished), and severe combined immunodeficiency disease (Jezyk et al., 1989; Patterson et al., 1982). Dogs with particular autoimmune diseases also suffer from immunodeficiency. A high incidence of septicemia has been observed in dogs that were bred to develop systemic lupus erythematosus (SLE) (Quimby et al., 1979). Autoimmune hemolytic anemia (AHA) (Bull et al., 1971; Dodds, 1983; Klag et al., 1993), immune thrombocytopenic purpura (ITP) (Dodds, 1983, 1992; Waye, 1960), SLE (Grindem and Johnson, 1983; Monier et al., 1988; Quimby, 1981), rheumatoid arthritis (RA) (Bell et al., 1991; Carter et al., 1989; Quimby et al., 1978), Sjögren's syndrome (Kaswan et al., 1985; Quimby et al., 1979), autoimmune thyroiditis (Gosselin et al., 1982; Quimby et al., 1979; Rajatanavin et al., 1989; Thacker et al., 1992), and thyrogastric disease (Quimby et al., 1978) have been found in research dogs. Primary immunodeficiencies in dogs have also been associated with the absence of the third component of complement (Winkelstein et al., 1981); deficits in neutrophil function, including cyclic hematopoiesis (see page 100) (Knoll, 1992; Lund et al., 1967) and granulocytopathy (Knoll, 1992; Renshaw and Davis, 1979); dysregulation of interleukin-6 (DiBartola et al., 1990; Rivas et al., 1992); and deficiency of growth hormone (Roth et al., 1980). Clinical signs of these diseases are presented in Table 6.7.

All dogs with primary immunodeficiencies are predisposed to infection. Dogs with disorders associated primarily with hypogammmaglobulinemia, complement, or phagocytic function are predisposed to bacterial infection (Blum et al., 1985; Lund et al., 1967; Moroff et al., 1986; Renshaw and Davis, 1979). Those with disorders of cell-mediated immunity have increased susceptibility to fungi and viruses (Jezyk et al., 1989).

TABLE 6.7 Clinical Signs of Selected Primary Immunodeficiency and Autoimmune Diseases in Dogs

Immunologic Disease	Clinical Signs
Common variable immunodeficiency	Increased susceptibility to infectious diseases; clinical presentation after the age of 6 months
IgM deficiency	Increased susceptibility to bacterial diseases
Selective IgA deficiency	Increased susceptibility of some dogs to infectious diseases of mucosal surfaces, such as those of gastrointestinal, respiratory, and urogenital tracts
Severe combined immunodeficiency	Extreme susceptibility to bacterial, viral, and fungal infections; clinical presentation in first few weeks of life; death before reaching maturity
Autoimmune hemolytic anemia	Pallor, slight jaundice, splenomegaly, lymphadenopathy, weakness, and shortness of breath; profound anemia and recurrent episodes of hemolytic disease in approximately 50% of affected dogs
Immune thrombocytopenic purpura	Bruise easily, prolonged bleeding after trauma
Systemic lupus erythematosus	Rash, hemolytic anemia, immunothrombocytopenic purpura, polyarthritis, and proteinuria; females affected more frequently than males
Rheumatoid arthritis	Swollen painful joints—generally multiple small articular joints
Sjögren's syndrome	Keratoconjunctivitis sicca (dry eyes); corneal ulcers associated with dry eyes; excessive dental caries; inflamed gums; signs associated with hypothyroidism, including tendency to obesity, tendency to seek warm places, bilaterally symmetrical hair loss, and changes in skin thickness
Autoimmune (lymphocytic) thyroiditis	Signs associated with hypothyroidism, including tendency to obesity, tendency to seek warm places, bilaterally symmetrical hair loss, and changes in skin thickness
Thyrogastric disease	Signs associated with hypothyroidism, inappetence, megaloblastic anemia, and atrophic gastritis
Granulocytopathy	Increased susceptibility to bacterial infections
Dysregulation of interleukin-6	Familial Mediterranean fever, characterized by fever, synovitis, and renal failure
Deficiency of growth hormone	Small body stature; generalized increase in susceptibility to infectious diseases

Husbandry and Veterinary Care

Immunodeficient dogs pose special management problems. Immune diseases must be diagnosed, their prognosis determined, and their therapy monitored. A number of tests have been developed for those purposes, including tests that assay T- and B-cell function (Ladiges et al., 1988, 1989), identify serologic markers of autoimmune diseases (Kaplan and Quimby, 1983; Quimby et al., 1980), identify circulating immune complexes in rheumatic and neoplastic diseases (Carter et al., 1989; Terman et al., 1979), and assay phagocyte function (Smith and Lumsden, 1983).

The susceptibility of immunodeficient dogs to infectious diseases is handled in various ways. All immunodeficient dogs can benefit from an environment that minimizes contact with canine pathogens; however, for some of these conditions (e.g., severe combined immunodeficiency), cesarean derivation and maintenance in a gnotobiotic chamber are required to ensure survival. Pups with humoral deficiencies born to normal dams profit from receiving maternal antibodies in colostrum, and their dams should be immunized before being bred to ensure that high concentrations of antibodies will be present. Adult dogs with humoral deficiencies can be helped by transfusions of normal or hyperimmune serum or plasma or by administration of purified gamma globulin. Some dogs that are genetically predisposed to autoimmune diseases can be spared clinical illness for years by housing them in gnotobiotic chambers; however, if they are moved to a conventional environment, they quickly develop autoimmune disease (Schwartz et al., 1978).

Dogs with autoimmune diseases should be carefully monitored and appropriately treated. Treatment might involve immunosuppressive therapy (e.g., for SLE, AHA, ITP, and RA), transfusions of red cells and platelets (for AHA and ITP), splenectomy (for AHA and ITP), renal dialysis (for SLE), administration of thyroxine (for autoimmune thyroiditis), administration of thyroxine and vitamin B_{12} (for thyrogastric disease), and administration of artificial tears (see the section on ophthalmologic disorders) and special dental care (for Sjögren's syndrome). Some dogs with growth hormone deficiency benefit from injections of thymosin (Roth et al., 1980). Bone marrow transplantation and systemic antibiotics are effective in treating dogs with neutrophil defects. Dogs with thrombocytopenia (as in SLE, ITP, or Evan's syndrome) are predisposed to bleeding and bruising and should be housed and maintained as described in the section on hematologic disorders. Preliminary studies suggest that oral levamisole therapy is efficacious in treating one type of canine common variable immunodeficiency that is associated with ulcerative colitis and a predisposition to adenocarcinoma of the intestine (A. Rivas, New York State College of Veterinary Medicine, Cornell University, Ithaca, N.Y., unpublished). Trials involving the use of colchicine to delay the onset of amyloidosis in dogs with interleukin-6

dysregulation are in progress (L. Tintle, Wurtsboro Veterinary Hospital, Wurtsboro, N.Y., unpublished). The care of dogs with C3 deficiency and dogs that have been exposed to total body irradiation and immunosuppressive drugs associated with organ transplantation is described below. Dogs should be immunized against known canine pathogens before being exposed to agents that will induce immunodeficiency.

Reproduction

In colonies where the objective is to reproduce dogs with SLE by selecting breeders with serologic evidence of the disorder (i.e., by using antinuclear antibody and LE-cell tests), many progeny develop autoimmune diseases not apparent in the parents (Monier et al., 1988; Quimby et al., 1979). That observation has led to the hypothesis that multiple genes control the susceptibility and specificity of autoimmune diseases (Monier et al., 1988; Quimby and Schwartz, 1978). In some cases, an unanticipated result is compromised fertility (e.g., immune-mediated aspermatogenesis), which necessitates the use of littermates or repeat breeding of the parents to continue the lineage (Quimby et al., 1978). Hypothyroidism caused by lymphocytic thyroiditis (Beierwaltes and Nishiyama, 1968; Gosselin et al., 1982; Mizejewski et al., 1971; Rajatanavin et al., 1989; Thacker et al., 1992) can lead to poor reproductive performance that can be corrected with thyroxine-replacement therapy. Details on monitoring blood thyroxine and oral supplementation have been published (DePaolo and Masoro, 1989; Ferguson, 1986). For some autoimmune diseases, such as immune-mediated aspermatogenesis, no therapy has been found.

Complement Deficiency

Clinical Features

Dogs deficient in the third component of complement (C3) are particularly susceptible to bacterial infections (Blum et al., 1985). They also develop a membranoproliferative glomerulonephritis, which can be detected histologically by the age of 1 year (Cork et al., 1991). Affected dogs are normally active and appear well; the only clinical sign of this renal disease is proteinuria. Renal disease progresses inexorably and culminates in a nephrotic syndrome with azotemia when the dogs are 6-8 years old.

Husbandry and Veterinary Care

Dogs deficient in C3 can be reared and housed in standard laboratory dog facilities. Because the dogs are susceptible to bacterial infections (Chick et al., 1984), animal technicians should be alert to any deviations from

normal behavior that might indicate illness (e.g., inappetence and lethargy). C3-deficient dogs that show these clinical signs must immediately be evaluated for increased body temperature and leukocytosis. Blood samples should be taken and submitted for culturing to identify and determine the antibiotic sensitivity of the microorganisms; however, treatment with intravenous bactericidal antibiotics should not await diagnosis but should begin as soon as clinical signs are detected and a blood sample has been drawn. Although that protocol undoubtedly results in overtreating and might preclude a definitive diagnosis, it will in most cases ensure the recovery and survival of the affected dog. If an invasive procedure (e.g., renal biopsy or placement of an indwelling catheter) is required, antibiotic prophylaxis should begin 24 hours beforehand, and it is essential to follow strict aseptic technique while performing the procedure.

The presence of proteinuria can be detected by testing for total-protein excretion in the urine over a 24-hour period, and renal biopsies can be used to evaluate the progression of renal disease. As dogs age, periodic measurements of total serum protein, albumin, and serum urea nitrogen can be used to identify dogs whose renal disease is becoming severe or those in which a nephrotic syndrome might lead to fluid accumulation in body cavities. Repeated blood transfusions or infusions of canine plasma are contraindicated because they exacerbate renal disease.

Reproduction

C3 deficiency is inherited as an autosomal recessive trait (Johnson et al., 1986; Winkelstein et al., 1982). Affected pups are produced by breeding heterozygous females with homozygous males. Homozygous females are fertile but have rarely produced viable young. Pups should be tested at birth, and the ones that are C3-deficient should be placed on antibiotic therapy for the first 4 days after birth. C3-deficient dogs do not respond normally to immunization; therefore, it is recommended that immunizations against the common canine pathogens be given at 2-week intervals until the pups are 18 weeks old (Krakowka et al., 1987; O'Neil et al., 1988; Winkelstein et al., 1986).

Organ Transplantation

Clinical Features

Dogs that are used in organ-transplantation studies must first be made immunodeficient. Immunosuppressive methods include total-body irradiation and administration of cytotoxic chemicals (Ladiges et al., 1989). Im-

munosuppressed dogs are very susceptible to infectious diseases and might have gastrointestinal tract problems.

Husbandry and Veterinary Care

Dogs that undergo experimental organ transplantation generally require intensive postoperative supportive care, the level of which depends on the transplantation procedure used and the degree of immunosuppression required to overcome graft rejection. Supportive care includes fluid therapy, blood and platelet transfusions, preoperative and postoperative administration of appropriate antibiotics, and intensive husbandry practices. Regular monitoring of white cells is critical for ascertaining health status and determining the necessity for treatment. Blood should be cultured if clinical signs suggest septicemia. Nutritional needs are critical for dogs undergoing bowel transplantation or for those suffering from gastrointestinal tract problems caused by the immunosuppressive procedures. Dogs might need to be housed individually in intensive-care facilities during early convalescence.

Dogs undergoing bone marrow transplantation are profoundly immunodeficient for 200-300 days after lethal total-body irradiation and successful marrow engraftment, and they require intensive supportive care (Ladiges et al., 1990). Recovery of granulocyte count and function is complete by the twenty-fifth day after engraftment; blood lymphocyte count does not return to normal until day 200. Antibody response to bacteriophage and sheep and chicken red cells is lower than normal during the first 200 days, with IgM being the primary isotype. Lymphocyte stimulation by phytohemagglutinin, the mixed-leukocyte reaction, and the response to first- and second-set skin grafts are impaired. Long-term survivors (dogs that survive more than 200 days) generally regain their health and are no longer more susceptible than normal to infectious diseases. The development of graft-versus-host disease and its treatment drastically affect recovery of the immune system and place the dogs at increased risk for contracting infections.

Lysosomal Storage Diseases

Clinical Features

Clinical manifestations of canine lysosomal storage diseases (LSDs) generally fall into three categories: severe neurologic signs, mainly skeletal signs, and a mixture of visceral, skeletal, and neurologic signs. The following discussion addresses techniques for managing dogs in each category, using a single LSD as an example. The techniques can be extended to manage dogs with other LSDs.

Fucosidosis. Fucosidosis is caused by a deficiency of α-L-fucosidase (Healy et al., 1984). Affected dogs exhibit mainly neurologic signs. By the age of 12 months, affected dogs show subtle behavioral changes and might have an overextended posture. From 12 to 18 months, they develop mild ataxia and hypermetria. Signs progress rapidly between the ages of 18 and 24 months to more severe deficits in gait, proprioceptive defects, hyperclonus, nystagmus, kyphosis, and a loss of learned behavior. The dogs become dull and unresponsive. Hearing and vision might be impaired. Signs in severely affected, 24- to 36-month-old dogs include severe incoordination, opisthotonos, muscle spasms, muscle wasting, circling, head tilt, abnormal pupillary light reflexes, dysphagia, and cranial nerve deficits. The dogs become severely obtunded and suffer from self-inflicted injury. If not euthanatized, they usually die by the age of 3 years.

Mucopolysaccharidosis VII. The majority of clinical signs in canine mucopolysaccharidosis VII (MPS VII), a condition caused by a deficiency of β-glucuronidase, are related to skeletal and joint abnormalities (Haskins et al., 1984). Progressive noninflammatory arthrosis develops, and joints become lax and deformed. By the age of 3-6 months, affected dogs are unable to stand, and the muscles of locomotion atrophy. Corneal clouding can lead to decreased vision in dogs with MPS VII, but the impairment is generally less severe than in dogs with MPS I. At the age of 15-22 months, MPS VII-affected dogs often become dull and lethargic and lose interest in their environment and in animal-care personnel. Those signs might be associated with progressive hydrocephalus.

Mucopolysaccharidosis I. Canine mucopolysaccharidosis I (MPS I), a condition caused by a deficiency of α-L-iduronidase, is most similar to the human MPS I phenotype of intermediate severity (Hurler's syndrome and Scheie's syndrome) (Shull et al., 1982). Clinical signs refer to visceral, skeletal, and mild neurologic injury. Dogs with MPS I appear normal at birth, although there is a higher than normal incidence of umbilical hernias. Affected pups remain generally healthy for 4-6 months and then show stunted growth, corneal clouding, and progressive, degenerative, noninflammatory joint disease caused by mucopolysaccharide deposition in synovial and periarticular tissues. Joint laxity caused by abnormalities in ligaments and tendons is also common and, in combination with the arthroses, causes decreased ambulation. Degeneration of intervertebral disks, collapse of disk spaces, vertebral and long-bone osteopenia, and spondylosis also develop. Mucopolysaccharide accumulation in heart valves and coronary arteries can cause rapidly progressing heart failure. Affected dogs remain alert and responsive until their death by natural causes or euthanasia, often between the ages of 2 and 3 years.

Husbandry and Veterinary Care

Dogs with LSD present unique and serious medical and husbandry problems. Proper care of these valuable, critically ill animal models requires compassion, diligence, hard work, and specialized knowledge of the diseases involved. Technicians must be well trained and observant.

Fucosidosis. As the clinical signs progress, affected dogs should be handled carefully to prevent injury. They should be fed, exercised, and housed separately from normal dogs. Severely ill dogs should be moved by carrying. Affected dogs should always be housed on a raised trampoline bed and kept dry during cage cleaning to prevent self-soiling and pressure sores. Particular attention should be given to dogs with long hair; they should be bathed weekly and clipped several times a year. Ears should be checked daily for signs of infection. Dogs with moderate to advanced disease should be fed more frequently, and canned or moistened dry food should be used to aid prehension. Dogs with advanced disease often have a poor appetite, and the addition of highly palatable foods assists in maintaining body weight. Excess dental tartar must be removed regularly. At the age of 2-3 years, motor and mental impairment will have progressed to the point that euthanasia will be indicated.

Mucopolysaccharidosis VII. MPS VII-affected dogs should be housed in cages with floors of coated wire mesh; this aids sanitation and helps to prevent decubital sores. Once the dogs are unable to walk, food and water intake must be carefully managed. Recumbent animals will usually eat and drink if pans of food and water are placed on the cage floor; however, hand feeding might become necessary. Euthanasia should be considered when a dog's response to human attention begins to diminish.

Mucopolysaccharidosis I. Except for surgical correction of umbilical hernias, special care is not usually required for dogs with MPS I that are less than 1 year old. However, as the disease progresses and the vertebral column deteriorates, the dogs become extremely fragile, and especially gentle handling is necessary when working with them or moving them between cages. Acute disk herniation can occur with even very minor trauma or inappropriate handling. Once skeletal disease has developed, exercise must be limited, and affected dogs must be protected from more rambunctious colony members. Decubital sores are a frequent consequence of the increase in time spent lying down. Housing affected dogs on shredded newspaper or elevated wire mesh provides both comfort and better sanitation.

Appetite generally remains normal, although hand feeding or varying the diet might become necessary, especially in dogs with pronounced cor-

neal clouding, impaired hearing, or the rare decrease in cerebral sensorium. Some dogs have enlarged tongues; however, prehension of food is generally not a problem. The teeth of dogs that are fed a diet composed mainly of canned food require periodic scaling of tartar.

MPS I-affected dogs are rarely maintained until they die naturally. By the age of 24-36 months, the symptoms of skeletal disease are generally so marked that euthanasia is indicated before debilitation becomes unacceptable.

Reproduction

Most LSDs can impair fertility in dogs. MPS I- and VII-affected males have sired litters by artificial insemination. Males with fucosidosis show copulatory behavior before they become severely uncoordinated, but they are infertile because of epididymal lesions, which probably impair spermatozoan capacitation. Females with fucosidosis are fertile but are very poor mothers; their pups usually must be fostered or hand-reared. Pups with LSDs are generally produced by breeding heterozygous carriers that are clinically normal.

Muscular Dystrophy

Clinical Features

A genetic disorder homologous to Duchenne's muscular dystrophy of humans—a devastating, fatal disorder predominantly of boys—occurs in various breeds of dogs. The disorder in dogs, which is inherited as a simple sex-linked recessive gene with full penetrance, is known as canine X-linked muscular dystrophy, and dogs with the condition are called *xmd* dogs. The mutation has been found in golden retrievers and rottweilers, and a similar mutation is suspected to have occurred in samoyeds, malamutes, and Irish terriers. The golden retriever is the best studied of the affected breeds, and the following discussion is based on data on this breed.

Both Duchenne's muscular dystrophy and canine X-linked muscular dystrophy are caused by a defect in the production of dystrophin, a skeletal muscle cytoskeletal protein. The mutation in the dystrophin gene results in massive continuing skeletal muscle degeneration that occurs from birth onward. In dogs, progressive cardiac muscle degeneration begins in hemizygous males at the age of about 6 months. Carrier bitches appear clinically normal but have subtle lesions in their cardiac muscles. Because of the homology to Duchenne's muscular dystrophy, the *xmd* dog can serve as an animal model for studies leading to better understanding of the pathogen-

esis of Duchenne's muscular dystrophy, as well as for studies designed to assess therapeutic approaches (Valentine et al., 1992).

Clinical signs of obvious weakness, muscle wasting, and abnormal gait appear in *xmd* dogs at the age of about 8 weeks. After that time, clinical signs progress, and they are most severe at the age of about 6 months, at which time the dogs have a markedly stiff, shuffling gait. There is frequently a severely abnormal posture, with carpal overextension, tarsal overflexion, and splaying of the limbs. The dogs are unable to open their jaws fully, their tongues are thickened and cannot be fully extended, and they frequently drool excessively. After the age of 6 months, the clinical disease appears to stabilize, and many dogs seem to gain strength as they age. However, there is still a progressive degeneration and fibrosis of cardiac muscle that results in the characteristic Duchenne-type cardiomyopathy.

Husbandry and Veterinary Care

Dystrophic dogs do not require special caging. Shavings provide a soft, warm surface, but the shavings must be free of dust so that the dogs do not inhale particles and develop granulomatous pneumonia. Temperature and humidity must be carefully controlled. Older dystrophic dogs should be monitored carefully for signs of cardiac failure. Treatment for heart failure has been described (Fraser et al., 1991). Euthanasia should be considered when treatment fails to alleviate clinical signs (e.g., when the dog has difficulty breathing and when fluid accumulates in the abdomen).

Dystrophic dogs require high-calorie food that is easy to prehend and swallow because of the weakness of their tongue, jaw, and esophageal muscles. Canned food mixed with moistened dry food seems to constitute an adequate diet, but careful monitoring of food intake and weight is necessary. Regurgitation of food is common because of the esophageal skeletal muscle dysfunction. Severely disabled dogs might not be able to use automatic watering devices and might have to be given water in bowls or buckets. Their water might need frequent changing because of a buildup of saliva.

Adequate exercise is crucial during the period of rapid growth. Although dystrophic dogs might prefer to lie down, restricted exercise will result in more severe joint contractures. The presence of a slightly more active dystrophic cagemate is ideal, provided that competition for food does not impair food intake. The kennel must have a nonslippery surface to provide traction, and daily release for exercise is advised. These dogs should not be forced to exercise, however, because it might lead to increased muscle damage.

Dystrophic dogs cannot groom themselves adequately. Regular brushing of their haircoat and clipping of overgrown toenails is required. To

prevent skin irritation, the mouth and jaw should be kept free of the saliva and food that accumulate.

Reproduction

Many dystrophic dogs survive to breeding age, and breeding colonies can be established. Some affected males are able to breed naturally; others are hampered by their physical disability and require artificial insemination techniques. An *xmd* male that breeds naturally might need assistance to remain upright once he has "tied" with the female. Breeding dystrophic bitches, which are produced by mating dystrophic males to carrier bitches, is possible but not advised. Pregnant dystrophic bitches require constant monitoring, are likely to have respiratory and cardiac complications, will require cesarean section, and might not be able to care for their pups adequately.

At whelping, a safe, warm environment and proper maternal care are essential for the survival of dystrophic pups. If dystrophic pups are stressed by cold, separation from the litter, or inability to compete with normal pups in a large litter, some of them will develop massive skeletal necrosis within the first few days of life. Once signs of severe weakness have developed in a pup, it is virtually impossible to save it. Severe diaphragmatic necrosis resulting in respiratory failure appears to be the cause of death. Dystrophic pups can be identified in the first week of life by their markedly increased serum concentrations of creatine kinase released from degenerating muscles. Dystrophic pups that survive the first week grow more slowly than their littermates. Euthanasia should be considered for pups that are too weak to nurse during the first week of life; tube feeding has not been successful in keeping such pups alive (B. A. Valentine, Department of Pathology, New York State College of Veterinary Medicine, Cornell University, Ithaca, N.Y., unpublished).

Neurologic Disorders

Clinical Features

Dogs with hereditary or induced neurologic disorders are often used to study equivalent human disorders. Clinical signs in these dogs include abnormal gait, hyperactivity, nervousness, tremors, convulsions, visual impairment, blindness, deafness, quadriplegia, and tetraplegia. Obviously, these dogs commonly require extra care to ensure that they are as comfortable as possible. Inherited canine neurologic diseases and their clinical signs have been reviewed by Cummings (1979) and Oliver and Lorenz

(1993); the pattern of inheritance of specific diseases has been discussed by Willis (1989).

Husbandry and Veterinary Care

Food and water must be placed where a neurologically impaired dog can find and reach them easily, and, if the dog is blind, placement should be consistent. That might require using water bowls instead of automatic waterers or, for dogs with severe impairment, intravenous or subcutaneous administration of fluids. Food might have to be placed in flat dishes, softened, or made into a gruel so that it can more easily be reached, masticated, and swallowed. Food and water intake should be monitored. Dogs should be weighed regularly to ensure that body weight is maintained. Nasogastric, lavage, pharyngotomy, or intragastric feeding might be required in some circumstances to provide adequate nutrition.

Dogs with sensory deficits can experience dysesthesias and might respond by chewing the affected limb or body part or another, more accessible body part. Several strategies can be used to deal with such behavior. Dogs should be closely monitored to detect the beginning of self-directed behaviors. A dog can sometimes be distracted by housing it where it has more external visual and social stimulation. If a nonaggressive cagemate can be identified, social housing might be sufficiently distracting—provided that the cagemate does not harass the affected dog or prevent it from eating and drinking. Toys, such as rawhide bones, might also be useful. If bandages must be used, they should not be too tight and should be checked regularly. Elizabethan collars or muzzles can be used to limit access to the body. Light tranquilization, if it does not interfere with the experimental protocol, might be helpful.

Dogs with sensory deficits might require extra or different bedding to prevent unintentional self-injury. The dogs' primary housing must be free of rough or sharp edges and projections. Dogs with motor deficits might have difficulty in positioning their bodies for urination and defecation. Sometimes all that is necessary is to provide flooring with better traction (e.g., plastic-coated grids or rubber mats). If necessary, research or animal-care personnel should assist the dog to position itself. Catheterization or manually expressing the bladder might be required to prevent urinary retention. Careful husbandry and nursing will avoid decubitus ulcers.

In dogs with respiratory deficits, the normal ability to thermoregulate by panting has been compromised. For these animals, exertion must be avoided and comfortable temperatures maintained.

Reproduction

Dogs with some neurologic disorders can reproduce, even though they are severely impaired. Such dogs usually need assistance for mating or require artificial insemination. Bitches with marked sensory or motor deficits or ataxia should be closely attended at parturition and while nursing to protect the pups from accidental injury. If the neurologic deficits of the dam interfere with her ability to care for her offspring, hand rearing or foster rearing will be required.

Ophthalmologic Disorders

Clinical Features

Dogs are affected by various ophthalmologic problems, either as inherent aspects of the research in which they are being used, as complications, or as acquired conditions unrelated to the research. Descriptions of canine eye diseases can be found in any standard text on veterinary ophthalmology (e.g., Gelatt, 1991; Helper, 1989). In the research setting, ocular problems that require special management techniques are visual impairment, painful ocular conditions, untoward sequelae of interfering with the eye's external protective mechanisms, and combinations of these conditions.

Blindness. Visual impairment in dogs usually cannot be measured precisely. For purposes of this discussion, *blindness* is used, in a loosely defined manner, to refer to any condition in which visual impairment is sufficient to interfere with a dog's ability to perform visually guided tasks or to exhibit normal visually guided behavior. In general, dogs maintained in a familiar environment adapt well to visual deficits that are congenital, are gradual in onset, or have been present for an extended time (weeks to months). A dog that has adapted to its blindness, that is maintained in a familiar environment, and that is not subjected to stressful experiences will move about actively and engage in all normal canine behavior. Its adaptation, or compensation, might be so successful that a naive observer will not recognize that it is blind.

Ocular pain. Painful ocular conditions fit broadly into three categories. External ocular pain is usually associated with corneal irritation and commonly causes obvious signs, such as blinking, excessive tearing, and redness. Uveal pain is caused by intraocular inflammation, which might not be evident without careful examination of the eye; uveal pain is usually more painful than corneal irritation. Glaucomatous pain is often the most insidious and most severe ocular pain. All these conditions are not only painful, but can threaten a dog's vision and the integrity of the affected eye.

Conditions associated with failure of the eye's external protective mechanisms. Untoward sequelae can arise from any condition that interferes with the eye's external defense mechanisms. These mechanisms depend on such funcitons as corneal sensitivity, lid movement, and tear production. Anything that reduces corneal sensation, interferes with lid movement, or lowers tear production can lead rapidly to painful ocular inflammation, impairment of vision, and loss of the affected eye. Common causes include anesthesia, radiation, surgical procedures, and drugs.

Husbandry and Veterinary Care

It is recommended that all experimental protocols involving dogs with ophthalmologic problems—whether the problems are "natural" (i.e., genetic), acquired, or induced—be reviewed by a veterinarian or a physician with training in ophthalmology (e.g., a veterinarian certified by the American College of Veterinary Ophthalmologists). Such protocols should include an adequate program for monitoring the dogs' ophthalmologic problems and written procedures for dealing with ocular emergencies.

Blindness. In spite of the ease with which dogs can adapt to blindness, they require special protection from a variety of environmental dangers, the more obvious of which are protruding objects, sharp edges, openings through which a dog might fall, and sources of electric or thermal injury. More insidious risks can arise because blind dogs lack the menace reflex, which normally protects the cornea from damage by causing the eyelids to blink in response to seen objects approaching the eye. Personnel responsible for the care and handling of blind dogs must be aware of these risks and keep them to a minimum and must watch for signs of acute or chronic corneal injury.

Dogs that have adapted to their blindness can become decompensated in response to rapid changes in their environment or other stressful experiences, such as anesthesia (e.g., for diagnostic, surgical, or experimental procedures), illness, and alterations in their daily routine. A decompensated chronically blind dog might look as though it has suddenly become blind and might exhibit behaviors compatible with a general stress reaction—from stiff-limbed hesitancy in walking and an apparent fear of its surroundings to anorexia or polydipsia, polyphagia, and polyuria. Similar signs can be observed in some dogs that have recently and rapidly lost their sight. Given time and a restricted, safe, and consistent environment, the blind dog will readapt and once again exhibit compensated normal behavior. Personnel responsible for the care and handling of blind dogs must be aware that these dogs need consistent familiar surroundings and that they might react adversely to stressful experiences. When approaching a blind dog, animal technicians should talk to it so that the dog will be more likely to perceive the approach as friendly.

Ocular pain. Ocular pain can vary from moderate to excruciating. Dogs in ophthalmologic research colonies are often at risk of developing ocular pain, either as a direct result of a study or as an unpredictable occasional side effect. In some cases, particularly if the pain is chronic or develops gradually, it will not be readily apparent without special examination procedures, especially if the observer is inexperienced. Personnel responsible for the care and handling of dogs used in ophthalmologic research should suspect that ocular pain is present when there is periocular soiling or when there are behavioral changes, such as decreased activity, decreased appetite, increased yawning, and changes in vocalization patterns.

Conditions associated with failure of the eye's external protective mechanisms. All protocols should be reviewed for potential adverse effects on external ocular defense mechanisms, and dogs subject to such risks should be monitored carefully for evidence of adverse effects.

Reproduction

Most dogs with ophthalmologic disorders can breed normally.

Orthopedic Disorders

Clinical Features

Dogs serve as models for both canine and human orthopedic diseases. Spontaneous bone and joint diseases of dogs have been reviewed (Lipowitz et al., 1993; Newton and Nunamaker, 1985; Whittick, 1990; Young, 1979). Orthopedic diseases can also be induced in dogs.

Husbandry and Veterinary Care

When inducing an orthopedic disease in dogs, one must first evaluate the dogs to be certain that natural bone and joint diseases are absent. Radiography is used to diagnose hip dysplasia, osteochondrosis, osteoarthritis, elbow dysplasia, and patellar luxation. These are considered heritable disorders because offspring of affected parents often have them and they occur in siblings.

Ideally, the surgical suite, the radiographic diagnostic facility, and an anesthesia recovery box lined with foam-rubber padding should be located near the primary housing facility. The floors of both the orthopedic research facility and the primary housing should be kept dry and have a nonslippery surface to provide good, steady footing.

The amount of food consumed should be monitored because excess body weight will exacerbate orthopedic conditions. Limiting food consumption during the growth period has been shown to reduce signs of orthopedic disease in dogs that mature at greater than 30 lb (Kealy et al., 1992). Dogs that refuse to eat because of pain might require a palatable high-energy food to maintain body weight. Human socialization is desirable to allow caregivers to detect abnormalities more readily and to facilitate handling and, when necessary, treatment.

Mild exercise, such as walking, is beneficial to keep muscles limber, promote bone formation, and increase lubrication and nutrition of joints. However, excessive exercise aggravates pain and causes further bone or joint damage. Anti-inflammatory drugs, given with food, can be used to relieve pain. Glucocorticosteroids, although potent anti-inflammatory agents that relieve pain, can also accelerate disease progression and should be used only in advanced cases of joint disease. Warm packs can ease the pain of chronic osteoarthritis. Dogs affected with skeletal diseases should be kept warm and dry, although pain associated with a recent injury can be eased by applying crushed ice in a plastic bag to the affected region.

Reproduction

Dogs with joint and bone diseases can generally be bred, although it might be necessary to guide and hold a male affected with moderate or severe hip dysplasia. If the orthopedic problem is so severe that mating is not possible, artificial insemination can be used.

Radiation Injury

Clinical Features

Radiation is commonly used in experimental protocols involving dogs. Total-body irradiation (TBI) is generally delivered by a cobalt-60 source or medical x-ray therapy machine. Doses of radiation up to 2 Gy can result in signs of illness related to mild gastrointestinal toxicity and decreased white-cell counts. At doses of 2-4 Gy, signs become progressively more severe. Doses greater than 4 Gy cause destruction of bone marrow, loss of circulating blood cells, immunosuppression, increased tendency to bleed, and moderate to severe gastrointestinal toxicity. Bone-marrow transplantation can prevent severe clinical signs and death in dogs. The high radiation doses are similar to the doses that human transplantation patients receive.

Several side effects occur in dogs that survive for long periods after TBI and bone-marrow rescue (Ladiges et al., 1989): pancreatic fibrosis,

malabsorption and malnutrition, radiation-induced cataracts, and malignancies. A consistent finding is graying of the hair.

Radionuclides that are ingested, inhaled, or injected rarely produce signs of illness. However, knowledge of the chemical form and metabolism of the radionuclide is necessary to determine possible side effects. For example, inhaled particles of oxides of cesium-144 are relatively insoluble in the lungs and potentially remain there for some time. Signs of radiation pneumonitis might then be expected (Mauderly et al., 1980). Conversely, strontium-90 as a chloride is relatively soluble in the lungs. When inhaled, it is translocated to the bones, where it can cause prolonged thrombocytopenia and neutropenia (Gillett et al., 1987).

Types of radiation. Radiation emissions can be alpha particles, beta particles, gamma rays, and x rays. The distinctions between those emissions are important for providing care for laboratory animals.

Alpha emissions from radionuclides, such as plutonium or americium, are generally high-energy emissions, but they travel very short distances in tissue. These radionuclides are rarely used in animals unless the study is specifically intended to assess metabolic or biologic effects of alpha emissions. No special precautions are needed for direct contact with animals contaminated with alpha-particle-emitting radionuclides because the radiation energy is absorbed within the animals' tissues. However, personnel should wear disposable clothing, shoe covers, gloves, eye protection, and respiratory protection to prevent inadvertent ingestion of, inhalation of, or wound contamination with alpha particles from contaminated feces, urine, bedding, cleaning water, or surfaces.

Beta-emitting radionuclides, such as cesium-144 and strontium-90, penetrate farther into animal tissues than alpha particles but still only a short distance. The same precautions should be taken as are taken for alpha particles. Dogs can usually be handled without taking further precautions 10-12 days after administration of radionuclides.

Gamma rays and x rays from internally deposited radionuclides penetrate tissues for considerable distances. These emissions can cause some radiation exposure of personnel, and it is important to know the potential exposure levels. These are generally low-energy kinds of radiation with short half-lives. Procedures for monitoring radiation must be in place to be certain that exposures of personnel are within accepted standards. The facility radiation-protection officer should participate in planning of animal-care procedures.

Disposal of radioactive wastes is regulated by both federal and state governments. It is important to have procedures in place for collecting, packaging, and labeling radioactive wastes before studies are initiated.

Biohazards associated with radioactivity. Dogs exposed to external radiation sources do not pose a hazard to personnel once exposure is complete; the concern is for the effects on the health of the exposed animals. However, dogs that are administered radionuclides by ingestion, injection, or inhalation might present a continuing hazard to personnel because the radionuclide will be excreted in feces, in urine, and in some instances in exhaled air for some period after exposure. Standard operating procedures must be developed and followed for collecting and disposing of all contaminated materials to protect animals and personnel. Animal health is of immediate concern only when large quantities of radionuclides are given.

Husbandry and Veterinary Care

Dogs exposed to external radiation can be housed in the usual manner (see Chapter 3); however, it is critical that immunosuppressed dogs be protected from other dogs that might harbor pathogens. Dogs given internally deposited radionuclides should be housed individually. To facilitate collection of contaminated excreta and cage-cleaning water, the cages should be designed for collection of urine and feces and should be easy to clean. Dog rooms must have adequate ventilation, and ventilated air should not be recirculated. It might also be necessary to filter exhaust air. To prevent cross-contamination and simplify monitoring, it is recommended that dogs exposed to the same radionuclide be housed in the same room.

Clinical observations and frequent peripheral-blood-cell counts are useful for monitoring dogs exposed to large doses of radiation. Treatment for reduced numbers of blood cells is supportive, and euthanasia should be considered if illness becomes too severe. Marrow "rescue" can prevent severe illness. Supportive care should consist of aggressive antibiotic and fluid therapy, and a semiliquid diet is necessary during the immediate post-irradiation period. Euthanasia should be considered in long-term survivors experiencing pancreatic fibrosis, malignancies, or pneumonitis.

Reproduction

Dogs that have received TBI are usually sterile. Lower doses of radiation have variable effects on reproduction.

Gene Therapy

Gene therapy can be used to correct inborn errors of metabolism, hemoglobinopathies, and blood factor A deficiencies; to insert genes into normal cells of the host (e.g., marrow stem cells) to increase their resistance to the toxic effects of chemotherapy; to introduce genes into cancer cells

that will restore suppressor-gene function or neutralize the function of activated oncogenes; and to induce tolerance to transplantation antigens by transferring genes that code for such antigens (Anderson, 1984). The use of the dog as a preclinical, large, random-bred animal model has set the stage for clinical gene therapy. A number of target tissues for gene therapy have been used; this section will cover three of them.

Hematopoietic Stem Cells

In preparation for gene transfer, marrow is aspirated while the dog is under general anesthesia. The hair over the shoulder and hip joints is clipped. The skin is cleaned with povidone iodine, washed with 70 percent ethyl alcohol, and cleansed with sterile Ringer's solution. Under sterile conditions, a needle 20 cm long and 2.5 mm in internal diameter is inserted into the marrow cavity through the proximal intertubercular groove of the humerus or trochanteric fossa of the femur. The needle is then connected with polyvinyl tubing to a suction flask, and marrow is aspirated by placing a suction flask, which contains tissue-culture medium and preservative-free heparin, under negative pressure with a pump. The procedure can be completed on all four limbs in approximately 20 minutes, during which 70-80 ml of a mixture of blood and bone marrow is collected. The marrow suspension is then passed through stainless-steel screens with 0.307- and 0.201-mm mesh diameters. A 1 ml sample is taken for marrow cell counts, and the remainder of the marrow is placed in plastic containers. The aspiration procedure is well tolerated without any sequelae. Dogs are capable of walking unimpaired after recovery from anesthesia.

Nucleated marrow cells are then cocultivated with virus-producing packaging cells at a ratio of 2:1 for 24 hours in 850-ml roller bottles. The gene-containing vector is replication-defective. Retrovirus-producing packaging cells are seeded in roller bottles 48 hours before the addition of marrow and are cultured in vitro with established techniques. After cocultivation, marrow cells are used to boost long-term cultures established 1 week earlier. The cultures are harvested after 6 days of incubation, and marrow cells are carefully removed without dislodging the virus-producing packaging cells, washed, resuspended in serum-free medium, and infused intravenously into the dog from which the marrow was taken.

In preparation for the infusion, the dog is exposed to total-body irradiation to create room for the infused marrow to seed. Total-body irradiation is administered at doses of 4-10 Gy and is usually delivered at a rate of 7 cGy/minute from two opposing cobalt-60 sources. For that purpose, an unanesthetized dog is housed in a polyurethane cage that is midway between the two cobalt-60 sources. The long axis of the cage is perpendicular to a line between the sources. After irradiation, the dog is returned to the

animal-care facility for supportive care. Total-body irradiation can cause nausea, vomiting, and diarrhea. Its destruction of normal marrow leads to a disappearance of red cells, white cells, and platelets. The temporary absence of those blood components produces a risk of anemia, infection, and bleeding that persists unless the dog receives a marrow graft and the graft begins to function. Dogs are monitored daily and receive parenteral fluids and electrolytes as required. Appropriate preoperative and postoperative antibiotics are routinely used to prevent and treat infections. Platelet and red-cell transfusions are given as needed. Marrow-graft function is monitored by evaluating daily blood counts.

The success of gene transfer can be assessed by repeated aspiration of marrow under general anesthesia and examination of the samples for the appropriate marker gene with culture techniques, the polymerase chain reaction, or other appropriate methods (Stead et al., 1988). Peripheral blood cells can be tested in a similar manner, as can lymph node lymphocytes and pulmonary macrophages (Stead et al., 1988).

Skin Keratinocytes

Skin keratinocytes provide another good target for gene insertion. For some gene products, such as adenosine deaminase, gene transfer can take place in any replicating tissue. A 2 × 1.5-cm skin biopsy is obtained from the recipient under general anesthesia. Keratinocytes are derived from the biopsy material and cocultivated in vitro with replication-deficient retroviral vectors that contain the gene of interest. Keratinocytes are then cultured in a liquid-air interface culture, which gives rise to the various layers of skin in an in vitro system. After some time in culture, the skin grown in vitro is transplanted into a prepared bed on the flank of the dog under general anesthesia. The transplant site is treated with topical antibiotic powder, protected by nonadhering dressing, and inspected daily by the investigators. Generally, the skin grows in and is functional in 3-4 weeks. Punch biopsies of 2-3 mm allow assessment of gene transfer (Flowers et al., 1990).

Smooth Muscle Transplantation

Because of their location, genetically modified vascular smooth muscle cells can be particularly useful for the treatment of some diseases (e.g., hemophilia). Studies have demonstrated that vascular smooth muscle cells are easily obtained, cultured, and genetically modified and replaced and provide a good target tissue for gene therapy that involves both secreted and nonsecreted proteins (Lim et al., 1991). A segment of femoral artery or vein is surgically removed from a dog for preparation of smooth muscle cell cultures. The procedure of removing femoral artery and vein segments will

not compromise the dog, because there is extensive collateral circulation in this region. With the dog under general anesthesia, as long a segment of vessel as possible (at least 2 cm) is isolated from the circulation with ligatures. Any side branches in the two ends are permanently ligated before the vessel is removed. The smooth muscle cells are isolated, cultured, and infected with replication-defective amphotropic retroviruses that carry the genes of interest, in accordance with National Institutes of Health recombinant-DNA guidelines. The genetically modified smooth muscle cells are returned to the animal from which they were obtained. With the dog once again under general anesthesia, the transduced cells are seeded into the left and right carotid arteries and into the remaining femoral arteries (Lim et al., 1991).

REFERENCES

Ackerman, N., R. Burk, A. W. Hahn, and H. M. Hayes, Jr. 1978. Patent ductus arteriosus in the dog: A retrospective study of radiographic, epidemiologic, and clinical findings. Am. J. Vet. Res. 39:1805-1810.

Andersen, A. C., and M. E. Simpson. 1973. The Ovary and Reproductive Cycle of the Dog (Beagle). Los Altos, Calif.: Geron-X, Inc. 290 pp.

Anderson, W. F. 1984. Prospects for human gene therapy. Science 226:401-409.

Arbulu, A., S. N. Ganguly, and E. Robin. 1975. Tricuspid valvulectomy without prosthetic replacement: Five years later. Surg. Forum 26:244-245.

AVMA (American Veterinary Medical Association). 1993. 1993 Report of the AVMA Panel on Euthanasia. J. Am. Vet. Med. Assoc. 202:229-249.

Beierwaltes, W. H., and R. H. Nishiyama. 1968. Dog thyroiditis: Occurrence and similarity to Hashimoto's struma. Endocrinology 83:501-508.

Bell, S. C., S. D. Carter, and D. Bennet. 1991. Canine distemper viral antigens and antibodies in dogs with rheumatoid arthritis. Res. Vet. Sci. 50:64-68.

Ben, L. K., J. Maselli, L. C. Keil, and I. A. Reid. 1984. Role of the renin-angiotensin system in the control of vasopressin and ACTH secretion during the development of renal hypertension in dogs. Hypertension 6:35-41.

Bice, D. E., and B. A. Muggenburg. 1985. Effect of age on antibody responses after lung immunization. Am. Rev. Respir. Dis. 132:661-665.

Blum, J. R., L. C. Cork, J. M. Morris, J. L. Olson, and J. A. Winkelstein. 1985. The clinical manifestations of a genetically determined deficiency of the third component of complement in the dog. Clin. Immunol. Immunopathol. 34:304-315.

Bonagura, J. D., ed. 1986. Section 4: Cardiovascular diseases. Pp. 319-424 in Current Veterinary Therapy. IX. Small Animal Practice, R. W. Kirk, ed. Philadelphia: W. B. Saunders.

Bovée, K. C., M. P. Littman, F. Saleh, R. Beeuwkes, W. Mann, P. Koster, and L. B. Kinter. 1986. Essential hereditary hypertension in dogs: A new animal model. J. Hypertens. 4(Suppl. 5):S172-S173.

Brooks, D. P., and T. A. Fredrickson. 1992. Use of ameroid constrictors in the development of renin-dependent hypertension in dogs. Lab. Anim. Sci. 42:67-69.

Brooks, D. P., T. A. Fredrickson, P. F. Koster, and R. R. Ruffolo, Jr. 1991. Effect of the dopamine β-hydroxylase inhibitor, SK&F 102698, on blood pressure in the 1-kidney, 1-clip hypertensive dog. Pharmacology 43:90-95.

Brown-Séquard, E. 1856. Recherches expérimentales sur la physiologie et la pathologie des capsules surrénales. Arch. Gén. Méd. (Sér. 5)8(II):385-401.

Buchanan, J. W. 1992. Causes and prevalence of cardiovascular disease. Pp. 647-654 in Current Veterinary Therapy XI, R. W. Kirk and J. D. Bonagura, eds. Philadelphia: W. B. Saunders.

Bull, R. W., R. Schirmer, and A. J. Bowdler. 1971. Autoimmune hemolytic disease in the dog. J. Am. Vet. Med. Assoc. 159:880-884.

Campbell, K. L. 1991. Immunoglobulin A deficiency in the dog: A retrospective study of 155 cases (1983-1990). Canine Pract. 16(4):7-11.

Capen, C. C., and S. L. Martin. 1989. The thyroid gland. Pp. 58-91 in Veterinary Endocrinology and Reproduction, 4th ed., L. E. McDonald and M. H. Pineda, eds. Philadelphia: Lea & Febiger.

Carlson, G. P. 1989. Fluid, electrolyte, and acid-base balance. Pp. 543-575 in Clinical Biochemistry of Domestic Animals, 4th ed., J. J. Kaneko, ed. San Diego: Academic Press.

Carter, S. D., S. C. Bell, A. S. M. Bari, and D. Bennett. 1989. Immune complexes and rheumatoid factors in canine arthritides. Ann. Rheum. Dis. 48:986-991.

Chester, D. K. 1987. The thyroid gland and thyroid diseases. Pp. 83-120 in Small Animal Endocrinology, F. H. Drazner, ed. New York: Churchill Livingstone.

Chick, T. W., S. E. Goldblum, N. D. Smith, C. Butler, B. J. Skipper, J. A. Winkelstein, L. C. Cork, and W. P. Reed. 1984. Pneumococcal-induced pulmonary leukostasis and hemodynamic changes: Role of complement and granulocytes. J. Lab. Clin. Med. 103:180-192.

Cork, L. C., J. M. Morris, J. L. Olson, S. Krakowka, A. J. Swift, and J. A. Winkelstein. 1991. Membranoproliferative glomerulonephritis in dogs with a genetically determined deficiency of the third component of complement. Clin. Immunol. Immunopathol. 60:455-470.

Cummings, J. F., ed. 1979. Part XIII: Nervous system. Pp. 107-178 in Spontaneous Animal Models of Human Disease, vol. II, E. J. Andrews, B. C. Ward, and N. H. Altman, eds. New York: Academic Press.

DePaolo, L. V., and E. J. Masoro. 1989. Endocrine hormones in laboratory animals. Pp. 279-308 in The Clinical Chemistry of Laboratory Animals, W. F. Loeb and F. W. Quimby, eds. New York: Pergamon Press.

De Reeder, E. G., N. Girard, R. E. Poelmann, J. C. Van Munsteren, D. F. Patterson, and A. C. Gittenberger-de Groot. 1988. Hyaluronic acid accumulation and endothelial cell detachment in intimal thickening of the vessel wall: The normal and genetically defective ductus arteriosus. Am. J. Pathol. 132:574-585.

De Rick, A., F. M. Belpaire, M. G. Bogaert, and D. Mattheeuws. 1978. Plasma concentrations of digoxin and digitoxin during digitalization of healthy dogs and dogs with cardiac failure. Am. J. Vet. Res. 39:811-815.

DiBartola, S. P., M. J. Tarr, D. M. Webb, and U. Giger. 1990. Familial renal amyloidosis in Chinese Shar Pei dogs. J. Am. Vet. Med. Assoc. 197:483-487.

Dodds, W. J. 1983. Immune-mediated diseases of the blood. Adv. Vet. Sci. Comp. Med. 27:163-196.

Dodds, W. J. 1988. Third international registry of animal models of thrombosis and hemorrhagic diseases. ILAR News 30:R1-R32.

Dodds, W. J. 1989. Hemostasis. Pp. 274-315 in Clinical Biochemistry of Domestic Animals, 4th ed., J. J. Kaneko, ed. San Diego: Academic Press.

Dodds, W. J. 1992. Bleeding disorders. Pp. 765-777 in Handbook of Small Animal Practice, 2d ed., R. V. Morgan, ed. New York: Churchill Livingstone.

Dougherty, S. H. 1986. Implant infections. Pp. 276-289 in Handbook of Biomaterials Evaluation, A. F. von Recum, ed. New York: Macmillan.

Drazner, F. H. 1987a. The adrenal cortex. Pp. 201-277 in Small Animal Endocrinology, F. H. Drazner, ed. New York: Churchill Livingstone.

Drazner, F. H., ed. 1987b. Small Animal Endocrinology. New York: Churchill Livingston. 508 pp.

Eigenmann, J. E. 1985. Acromegaly. Model no. 311 in A Handbook: Animal Models of Human Disease, fascicle 14, C. C. Capen, T. C. Jones, and G. Migaki, eds. Washington, D.C.: Registry of Comparative Pathology, Armed Forces Institute of Pathology.

Eigenmann, J. E. 1989. Pituitary-hypothalamic diseases. Pp. 1579-1609 in Textbook of Veterinary Internal Medicine, vol. 2, 3rd ed., S. J. Ettinger, ed. Philadelphia: W. B. Saunders.

Ettinger, S. J., ed. 1989. Textbook of Veterinary Internal Medicine, vol. 2, 3rd. ed. Philadelphia: W.B. Saunders. 1,237 pp.

Eyster, G. E. 1992. Congenital diseases. Pp. 63-69 in Handbook of Small Animal Practice, 2d ed., R. V. Morgan, ed. New York: Churchill Livingstone.

Feldman, E. C. 1989. Adrenal gland disease. Pp. 1721-1774 in Textbook of Veterinary Internal Medicine, vol. 2, 3rd ed., S. J. Ettinger, ed. Philadelphia: W. B. Saunders.

Feldman, E. C., and R. W. Nelson. 1987. Canine and Feline Endocrinology and Reproduction. Philadelphia: W. B. Saunders. 564 pp.

Felsburg, P. J., L. T. Glickman, and P. F. Jezyk. 1985. Selective IgA deficiency in the dog. Clin. Immunol. Immunopathol. 36:297-305.

Ferguson, D. C. 1986. Thyroid hormone replacement therapy. Pp. 1018-1019 in Current Veterinary Therapy IX, R. W. Kirk, ed. Philadelphia: W. B. Saunders.

Ferrario, C. M., C. Blumle, G. R. Nadzam, and J. W. McCubbin. 1971. An externally adjustable renal artery clamp. J. Appl. Physiol. 31:635-637.

Fischer, C. A. 1989. Geriatric ophthalmology. Vet. Clinics N. Am. 19(1):103-123.

Fixler, D. E., J. P. Archie, D. J. Ullyot, G. D. Buckberg, and J. I. E. Hoffman. 1973. Effects of acute right ventricular systolic hypertension on regional myocardial blood flow in anesthetized dogs. Am. Heart J. 85:491-500.

Flowers, M. E. D., M. A. R. Stockschlaeder, F. G. Schuening, D. Niederwieser, R. Hackman, A. D. Miller, and R. Storb. 1990. Long-term transplantation of canine keratinocytes made resistant to G418 through retrovirus-mediated gene transfer. Proc. Natl. Acad. Sci. USA 87:2349-2353.

Fraser, C. M., J. A. Bergeron, A. Mays, and S. E. Aiello, eds. 1991. Heart disease. Pp. 40-52 in The Merck Veterinary Manual: A Handbook of Diagnosis, Therapy, and Disease Prevention for the Veterinarian, 7th ed. Rahway, N.J.: Merck & Co.

Gardner, T. J., and D. L. Johnson. 1988. Cardiovascular system. Pp. 74-113 in Experimental Surgery and Physiology: Induced Animal Models of Human Disease, M. M. Swindle and R. J. Adams, eds. Baltimore: Williams & Wilkins.

Gelatt, K. N., ed. 1991. Veterinary Ophthalmology, 2d ed. Philadelphia: Lea & Febiger. 765 pp.

Gillett, N. A., B. A. Muggenburg, B. B. Boecker, F. F. Hahn, F. A. Seiler, A. H. Rebar, R. K. Jones, and R. O. McClellan. 1987. Single inhalation exposure to $^{90}SrCl_2$ in the beagle dog: Hematological effects. Radiat. Res. 110:267-288.

Gittenberger-de Groot, M. D., J. L. M. Strengers, M. Mentink, R. E. Poelmann, and D. F. Patterson. 1985. Histologic studies on normal and persistent ductus arteriosus in the dog. J. Am. Coll. Cardiol. 6:394-404.

Goldston, R. T., ed. 1989. Geriatrics and gerontology. Vet. Clin. N. Am. 19(1):1-202.

Gosselin, S. J., C. C. Capen, S. L. Martin, and S. Krakowka. 1982. Autoimmune lymphocytic thyroiditis in dogs. Vet. Immunol. Immunopathol. 3:185-201.

Grindem, C. B., and K. H. Johnson. 1983. Systemic lupus erythematosus: Literature review and report of 42 new canine cases. J. Am. Anim. Hosp. Assoc. 19:489-503.

Guyton, A. C. 1991. Dominant role of the kidneys in long-term regulation of arterial pressure

and in hypertension: The integrated system for pressure control. Pp. 205-220 in Textbook of Medical Physiology, 8th ed. Philadelphia: W. B. Saunders.

Haley, P. J., F. F. Hahn, B. A. Muggenburg, and W. C. Griffith. 1989. Thyroid neoplasms in a colony of beagle dogs. Vet. Pathol. 26:438-441.

Hall, R. L., and U. Giger. 1992. Disorders of red blood cells. Pp. 715-733 in Handbook of Small Animal Practice, 2d ed., R. V. Morgan, ed. New York: Churchill Livingstone.

Harvey, J. W. 1989. Erythrocyte metabolism. Pp. 186-234 in Clinical Biochemistry of Domestic Animals, 4th ed., J. J. Kaneko, ed. San Diego: Academic Press.

Haskins, M. E., R. J. Desnick, N. DiFerrante, P. F. Jezyk, and D. F. Patterson. 1984. ß-glucuronidase deficiency in a dog: A model of human mucopolysaccharidosis VII. Pediatr. Res. 18:980-984.

Healy, P. J., B. R. H. Farrow, F. W. Nicholas, K. Hedberg, and R. Ratcliffe. 1984. Canine fucosidosis: A biochemical and genetic investigation. Res. Vet. Sci. 36:354-359.

Hegreberg, G. A., G. A. Padgett, J. R. Gorham, and J. B. Henson. 1969. A connective tissue disease of dogs and mink resembling the Ehlers-Danlos syndrome of man. II. Mode of inheritance. J. Hered. 60:249-254.

Hegreberg, G. A., G. A. Padgett, R. L. Ott, and J. B. Henson. 1970. A heritable connective tissue disease of dogs and mink resembling the Ehlers-Danlos syndrome of man. I. Skin tensile strength properties. J. Invest. Dermatol. 54:377-380.

Helper, L. C. 1989. Magrane's Canine Ophthalmology, 4th ed. Philadelphia: Lea & Febiger. 297 pp.

Hsu, W. H., and M. H. Crump. 1989. The adrenal gland. Pp. 202-230 in Veterinary Endocrinology and Reproduction, 4th ed., L. E. McDonald and M. H. Pineda, eds. Philadelphia: Lea & Febiger.

Järvinen, A.-K. 1981. Urogenital tract infection in the bitch. Vet. Res. Commun. 4:253-269.

Jezyk, P. F., P. J. Felsburg, M. E. Haskins, and D. F. Patterson. 1989. X-linked severe combined immunodeficiency in the dog. Clin. Immunol. Immunopathol. 52:173-189.

Johnson, J. P., R. H. McLean, L. C. Cork, and J. A. Winkelstein. 1986. Animal model: Genetic analysis of an inherited deficiency of the third component of complement in Brittany spaniel dogs. Am. J. Med. Genet. 25:557-562.

Kaneko, J. J. 1987. Critical review. Animal models of inherited hematologic disease. Clin. Chim. Acta 165:1-19.

Kaneko, J. J. 1989. Carbohydrate metabolism and its diseases. Pp. 44-85 in Clinical Biochemistry of Domestic Animals, 4th ed., J. J. Kaneko, ed. San Diego: Academic Press.

Kaplan, A. V., and F. W. Quimby. 1983. A radiolabeled staphylococcal protein A assay for detection of anti-erythrocyte IgG in warm agglutinin autoimmune hemolytic anemia of dogs and man. Vet. Immunol. Immunopathol. 4:307-317.

Kaswan, R. L., C. L. Martin, and D. L. Dawe. 1985. Keratoconjunctivitis sicca: Immunological evaluation of 62 canine cases. Am. J. Vet. Res. 46: 376-383.

Kealy, R. D., S. E. Olsson, K L. Monti, D. F. Lawler, D. N. Biery, R. W. Helms, G. Lust, and G. K. Smith. 1992. Effects of limited food consumption on the incidence of hipdysplasia in growing dogs. J. Am. Vet. Med. Assoc. 201:857-863.

Kesel, M. L., and D. H. Neil. 1990. Restraint and handling of animals. Pp. 1-30 in Clinical Textbook for Veterinary Technicians, 2d ed., D. M. McCurnin, ed. Philadelphia: W. B. Saunders.

Kirk, R. W., and S. I. Bistner. 1985. Metabolic emergencies. Pp. 138-149 in Handbook of Veterinary Procedures and Emergency Treatment, 4th ed. Philadelphia: W. B. Saunders.

Klag, A. R., U. Giger, and F. S. Shofer. 1993. Idiopathic immune-mediated hemolytic anemia in dogs: 42 cases (1986-1990). J. Am. Vet. Med. Assoc. 202:783-788.

Knight, D. H., D. F. Patterson, and J. Melbin. 1973. Constriction of the fetal ductus arteriosus induced by oxygen, acetylcholine, and norepinephrine in normal dogs and those genetically predisposed to persistent patency. Circulation 47:127-132.

Knoll, J. S. 1992. Disorders of white blood cells. Pp. 735-749 in Handbook of Small Animal Practice, 2d ed., R. V. Morgan, ed. New York: Churchill Livingstone.

Krakowka, S., L. C. Cork, J. A. Winklestein, and M. K. Axthelm. 1987. Establishment of central nervous system infection by canine distemper virus: Breach of the blood-brain barrier and facilitation by antiviral antibody. Vet. Immunol. Immunopathol. 17:471-482.

Kramer, J. W. 1981. Inherited early-onset, insulin-requiring diabetes mellitus in keeshond dogs. Am. J. Pathol. 105:194-196.

Ladiges, W. C., H. J. Deeg, J. A. Aprile, R. F. Raff, F. Schuening, and R. Storb. 1988. Differentiation and function of lymphohemopoietic cells in the dog. Pp. 307-335 in Differentiation Antigens in Lymphohemopoietic Tissues, M. Miyasaka and Z. Trnka, eds. New York: Marcel Dekker.

Ladiges, W. C., R. Storb, T. Graham, and E. D. Thomas. 1989. Experimental techniques used to study the immune system of dogs and other large animals. Pp. 103-133 in Methods of Animal Experimentation, vol. VII, part C, W. I. Gay and J. E. Heavner, eds. New York: Academic Press.

Ladiges, W. C., R. Storb, and E. D. Thomas. 1990. Canine models of bone marrow transplantation. Lab. Anim. Sci. 40:11-15.

Lage, A. L., N. A. Gillett, R. F. Gerlach, and E. N. Allred. 1989. The prevalence and distribution of proliferative and metaplastic changes in normal appearing canine bladders. J. Urol. 141:993-997.

Lange, J., B. Brockway, and S. Azar. 1991. Telemetric monitoring of laboratory animals: An advanced technique that has come of age. Lab Anim. 20(7):28-33.

Lim, C. S., G. D. Chapman, R. S. Gammon, J. B. Muhlestein, R. P. Bauman, R. S. Stack, and J. L. Swain. 1991. Direct in vivo gene transfer into the coronary and peripheral vasculatures of the intact dog. Circulation 83:2007-2011.

Lipowitz, A. J., D. D. Caywood, C. D. Newton, and M. E. Finch. 1993. Small Animal Orthopedics Illustrated: Surgical Approaches and Procedures. St. Louis: Mosby. 336 pp.

Lowseth, L. A., N. A. Gillett, R. F. Gerlach, and B. A. Muggenburg. 1990a. The effects of aging on hematology and serum chemistry values in the beagle dog. Vet. Clin. Pathol. 19(1):13-19.

Lowseth, L. A., R. F. Gerlach, N. A. Gillett, and B. A. Muggenburg. 1990b. Age-related changes in the prostate and testes of the beagle dog. Vet. Pathol. 27:347-353.

Lund, J. E., G. A. Padgett, and R. L. Ott. 1967. Cyclic neutropenia in grey collie dogs. Blood 29:452-461.

MacVean, D. W., A. W. Monlux, P. S. Anderson, Jr., S. L. Silberg, and J. F. Rozel. 1978. Frequency of canine and feline tumors in a defined population. Vet. Pathol. 15:700-715.

Maggio-Price, L., C. L. Emerson, T. R. Hinds, F. F. Vincenzi, and W. R. Hammond. 1988. Hereditary nonspherocytic hemolytic anemia in beagles. Am. J. Vet. Res. 49:1020-1025.

Mann, W. A., M. S. Landi, E. Horner, P. Woodward, S. Campbell, and L. B. Kinter. 1987. A simple procedure for direct blood pressure measurements in conscious dogs. Lab. Anim. Sci. 37:105-108.

Mauderly, J. L., and F. F. Hahn. 1982. The effects of age on lung function and structure of adult animals. Adv. Vet. Sci. Comp. Med. 26:35-77.

Mauderly, J. L., B. A. Muggenburg, F. F. Hahn, and B. B. Boecker. 1980. The effects of inhaled ^{144}Ce on cardiopulmonary function and histopathology of the dog. Radiat. Res. 84:307-324.

McCarthy, C. R., and J. G. Miller. 1990. OPRR Reports, May 21, 1990. Available from Office for Protection from Research Risks (OPRR), Building 31, Room 5B59, National Institutes of Health, Bethesda, MD 20892.

McDonald, L. E., and M. H. Pineda, eds. 1989. Veterinary Endocrinology and Reproduction, 4th ed. 571 pp.

Meuten, D. J., C. C. Capen, G. J. Kociba, and B. J. Cooper. 1982. Hypercalcemia of malignancy. Hypercalcemia associated with an adenocarcinoma of the apocrine glands of the anal sac. Am. J. Pathol. 108:366-370.

Meuten, D. J., C. C. Capen, and G. J. Kociba. 1986. Hypercalcemia of malignancy. Supplemental update, 1986: Model no. 143 in A Handbook: Animal Models of Human Disease, fascicle 15, C. C. Capen, T. C. Jones, and G. Migaki, eds. Washington, D.C.: Registry of Comparative Pathology, Armed Forces Institute of Pathology.

Mill, A. B., and K. L. Campbell. 1992. Concurrent hypothyroidism, IgM deficiency, impaired T-cell mitogen response, and multifocal cutaneous squamous papillomas in a dog. Canine Pract. 17(2):15-21.

Milne, K. L., and H. M. Hayes, Jr. 1981. Epidemiologic features of canine hypothyroidism. Cornell Vet. 73:3-14.

Minor, R. R., J. A. M. Wootton, D. J. Prockop, and D. F. Patterson. 1987. Genetic diseases of connective tissues in animals. Curr. Probl. Dermatol. 17:199-215.

Mizejewski, G. J., J. Baron, and G. Poissant. 1971. Immunologic investigations of naturally occurring canine thyroiditis. J. Immunol. 107:1152-1160.

Monier, J. C., C. Fournel, M. Lapras, M. Dardenne, T. Randle, and C.M. Fontaine. 1988. Systemic lupus erythematosus in a colony of dogs. Am. J. Vet. Res. 49:46-51.

Mordes, J. P., and A. A. Rossini. 1985. Animal models of diabetes mellitus. Pp. 110-137 in Joslin's Diabetes Mellitus, 12th ed., A. Marble, L. P. Krall, R. F. Bradley, A. R. Christlieb, and J. S. Soeldner, eds. Philadelphia: Lea & Febiger.

Morgan, R. V, ed. 1992. Handbook of Small Animal Practice, 2d ed. New York: Churchill Livingstone. 1,513 pp.

Moroff, S. D., A. I. Hurvitz, M. E. Peterson, L. Saunders, and K. E. Noone. 1986. IgA deficiency in Shar-Pei dogs. Vet. Immunol. Immunopathol. 13:181-188.

Nakano, K., M. M. Swindle, F. G. Spinale, K. Ishihara, S. Kanazawa, A. Smith, R. W. W. Biederman, L. Clamp, Y. Hamada, M. R. Zile, and B. A. Carabello. 1991. Depressed contractile function due to canine mitral regurgitation improves after correction of the volume overload. J. Clin. Invest. 87:2077-2086.

Nelson, A. A., and G. Woodard. 1949. Severe adrenal cortical atrophy (cytotoxic) and hepatic damage produced in dogs by feeding 2,2-bis(parachlorophenyl)-1,1-dichloroethane (DDD or TDE). Arch. Pathol. 48:387-394.

Nelson, R. W. 1989. Disorders of the endocrine pancreas. Pp. 1676-1720 in Textbook of Veterinary Internal Medicine, vol. 2, 3rd ed., S. J. Ettinger, ed. Philadelphia: W. B. Saunders.

Newton, C. D., and D. M. Nunamaker. 1985. Textbook of Small Animal Orthopaedics. Philadelphia: J. B. Lippincott. 1,140 pp.

Nichols, R., and M. E. Peterson. 1992. Hypoadenocorticism. Pp. 531-534 in Handbook of Small Animal Practice, 2d ed., R. V. Morgan , ed. New York: Churchill Livingstone.

NRC (National Research Council), Institute of Laboratory Animal Resources, Committee on Care and Use of Laboratory Animals. 1985. Guide for the Care and Use of Laboratory Animals. NIH Pub. No. 86-23. Washington, D.C.: U.S. Department of Health and Human Services. 83 pp.

NRC (National Research Council), Institute of Laboratory Animal Resources, Committee on Immunologically Compromised Rodents. 1989. Introduction. Pp. 1-35 in Immunodeficient Rodents: A Guide to Their Immunobiology, Husbandry, and Use. Washington, D.C.: National Academy Press.

Ogilive, G. K., W. M. Haschek, S. J. Withrow, R. C. Richardson, H. J. Harvey, R. A. Henderson, J. D. Fowler, A. M. Norris, J. Tomlinson, D. McCaw, J. S. Klausner, R. W. Reschke, and B. C. McKiernan. 1989. Classification of primary lung tumors in dogs: 210 cases (1975-1985). J. Am. Vet. Med. Assoc. 195:106-108.

O'Kane, H. O., A. S. Geha, R. E. Kleiger, T. Abe, M. T. Salaymeh, and A. B. Malik. 1973. Stable left ventricular hypertrophy in the dog. Experimental production, time course, and natural history. J. Thorac. Cardiovasc. Surg. 65:264-271.

Oliver, J. E. Jr., and M. D. Lorenz. 1993. Appendix. Pp. 374-393 in Handbook of Veterinary Neurology, 2d ed. Philadelphia: W. B. Saunders.

O'Neil, K. M., H. D. Ochs, S. R. Heller, L. C. Cork, J. M. Morris, and J. A. Winkelstein. 1988. Role of C3 in humoral immunity. Defective antibody production in C3-deficient dogs. J. Immunol. 140:1939-1945.

Patterson, D. F. 1968. Epidemiologic and genetic studies of congenital heart disease in the dog. Circ. Res. 23:171-202.

Patterson, D. F. 1984. Two hereditary forms of ventricular outflow obstruction in the dog: Pulmonary valve dysplasia and discrete subaortic stenosis. Pp. 43-63 in Congenital Heart Disease: Causes and Processes, J. J. Nora and A. Takao, eds. Mt. Kisco, N.Y.: Future Publishing Co.

Patterson, D. F., R. L. Pyle, J. W. Buchanan, E. Trautvetter, and D. A. Abt. 1971. Hereditary patent ductus arteriosus and its sequelae in the dog. Circ. Res. 29:1-13.

Patterson, D. F., R. L. Pyle, L. Van Mierop, J. Melbin, and M. Olson. 1974. Hereditary defects of the conotruncal septum in keeshond dogs: Pathologic and genetic studies. Am. J. Cardiol. 34:187-205.

Patterson, D. F., M. E. Haskins, and W. R. Schnarr. 1981. Hereditary dysplasia of the pulmonary valve in beagle dogs: Pathologic and genetic studies. Am. J. Cardiol. 47:631-641.

Patterson, D. F., M. E. Haskins, and P. F. Jezyk. 1982. Models of human genetic disease in domestic animals. Adv. Hum. Genet. 12:263-339.

Patterson, D. F., T. Pexieder, W. R. Schnarr, T. Navratil, and R. Alaili. 1993. A single major-gene defect underlying cardiac conotruncal malformations interferes with myocardial growth during embryonic development: Studies in the CTD line of keeshond dogs. Am. J. Hum. Genet. 52:388-397.

Petersen, J. C., R. R. Linartz, R. L. Hamlin, and R. E. Stoll. 1988. Noninvasive measurement of systemic arterial blood pressure in the conscious beagle dog. Fundam. Appl. Toxicol. 10:89-97.

Peterson, M. E., and D. C. Ferguson. 1989. Thyroid disease. Pp. 1632-1675 in Textbook of Veterinary Internal Medicine, vol. 2, 3rd ed., S. J. Ettinger, ed. Philadelphia: W. B. Saunders.

PHS (Public Health Service). 1986. Public Health Service Policy on Humane Care and Use of Laboratory Animals. Washington, D.C.: U.S. Department of Health and Human Services. 28 pp. Available from the Office for Protection from Research Risks, Building 31, Room 4B09, NIH, Bethesda, MD 20892.

Plechner, A. J. 1979. IgM deficiency in 2 doberman pinschers. Mod. Vet. Pract. 60:150.

Pyle, R. L., D. F. Patterson, and S. Chacko. 1976. The genetics and pathology of discrete subaortic stenosis in the Newfoundland dog. Am. Heart J. 92:324-334.

Quimby, F. W. 1981. Canine systemic lupus erythematosus. Pp. 175-184 in Immunologic Defects in Laboratory Animals, vol. 2, M. E. Gershwin and B. Merchant, eds. New York: Plenum Press.

Quimby, F. W., and R. S. Schwartz. 1978. The etiopathogenesis of systemic lupus erythematosus. Pathobiol. Annu. 8:35-59.

Quimby, F. W., C. Jensen, D. Nawrocki, and P. Scollin. 1978. Selected autoimmune diseases in the dog. Vet. Clin. N. Am. 8(4):665-682.

Quimby, F. W., R. S. Schwartz, T. Poskitt, and R. M. Lewis. 1979. A disorder of dogs resembling Sjögren's syndrome. Clin. Immunol. Immunopathol. 12:471-476.

Quimby, F. W., C. Smith, M. Brushwein, and R.W. Lewis. 1980. Efficacy of immunoserodiagnostic

procedures in the recognition of canine immunologic diseases. Am. J. Vet. Res. 41:1662-1666.

Rajatanavin, R., S.-L. Fang, S. Pino, P. Laurberg, L. Braverman, M. Smith, and L. P. Bullock. 1989. Thyroid hormone antibodies and Hashimoto's thyroiditis in mongrel dogs. Endocrinology 124:2535-2540.

Renshaw, H. W., and W. C. Davis. 1979. Canine granulocytopathy syndrome. An inherited disorder of leukocyte function. Am. J. Pathol. 95:731-744.

Rivas, A. L., L. Tintle, E. S. Kimball, J. Scarlett, and F. W. Quimby. 1992. A canine febrile disorder associated with elevated interleukin-6. Clin. Immunol. Immunopathol. 64:36-45.

Ross, L. A. 1989. Hypertensive disease. Pp. 2047-2056 in Textbook of Veterinary Internal Medicine, vol. 2, 3rd ed., S. J. Ettinger, ed. Philadelphia: W. B. Saunders.

Roth, J. A., L. G. Lomax, N. Altszuler, J. Hampshire, M. I. Kaeberle, M. Shelton, D. D. Draper, and A. E. Ledet. 1980. Thymic abnormalities and growth hormone deficiency in dogs. Am. J. Vet. Res. 41:1256-1262.

Schrader, L. A. 1988. Hypoadrenocorticism. Pp. 543-546 in Handbook of Small Animal Practice, 2d ed., R. V. Morgan, eds. New York: Churchill Livingstone.

Schwartz, R. S., F. W. Quimby, and J. André-Schwartz. 1978. Canine systemic lupus erythematosus: Phenotypic expression of autoimmunity in a closed colony. Pp. 287-294 in Genetic Control of Autoimmune Disease, N. R. Rose, P. Bigazzi, and N. Warner, eds. New York: Elsevier-North Holland.

Shull, R. M., R. J. Munger, E. Spellacy, C. W. Hall, G. Constantopoulos, E. F. Neufeld. 1982. Canine α-L-iduronidase deficiency: A model of mucopolysaccharidosis I. Am. J. Pathol. 109:244-248.

Smith, G. S., and J. H. Lumsden. 1983. Review of neutrophil adherence, chemotaxis, phagocytosis and killing. Adv. Vet. Immunol. 1982 12:177-236.

Stead, R. B., W. W. Kwok, R. Storb, and A. D. Miller. 1988. Canine model for gene therapy: Inefficient gene expression in dogs reconstituted with autologous marrow infected with retroviral vectors. Blood 71:742-747.

Swindle, M. M., F. G. Spinale, A. C. Smith, R. E. Schumann, C. T. Green, K. Nakano, S. Kanasawa, K. Ishihara, M. R. Zile, and B. A. Carabello. 1991. Anesthetic and postoperative protocols for a canine model of reversible left ventricular volume overload. J. Invest. Surg. 4:339-346.

Taylor, G. N., L. Shabestari, J. Williams, C. W. Mays, W. Angus, and S. McFarland. 1976. Mammary neoplasia in a closed beagle colony. Cancer Res. 36:2740-2743.

Terman, D. S., D. Moore, J. Collins, B. Johnston, D. Person, J. Templeton, R. Poser, and F. Quimby. 1979. Detection of immune complexes in sera of dogs with rheumatic and neoplastic diseases by ^{125}I-Clq binding test. J. Comp. Pathol. 89:221-227.

Thacker, E. L., K. R. Refsal, and R. W. Bull. 1992. Prevalence of autoantibodies to thyroglobulin, thyroxine, or triiodothyronine and relationship of autoantibodies and serum concentrations of iodothyronines in dogs. Am. J. Vet. Res. 53:449-453.

Tholen, M. A., and R. F. Hoyt, Jr. 1983. Oral pathology. Pp. 39-67 in Concepts in Veterinary Dentistry. Edwardsville, Kansas: Veterinary Medicine Publishing Co.

Valentine, B. A., N. J. Winand, D. Pradhan, N. S. Moise, A. de Lahunta, J. N. Kornegay, and B. J. Cooper. 1992. Canine X-linked muscular dystrophy as an animal model of Duchenne muscular dystrophy: A review. Am. J. Med. Genetics 42:352-356.

Van Mierop, L. H. S., D. F. Patterson, and W. R. Schnarr. 1977. Hereditary conotruncal septal defects in keeshond dogs: Embryologic studies. Am. J. Cardiol. 40:936-950.

Vlahakes, G. J., K. Turley, and J. I. E. Hoffman. 1981. The pathophysiology of failure in acute right ventricular hypertension: Hemodynamic and biochemical correlations. Circulation 63:87-95.

Waye, J. W. 1960. Idiopathic thrombocytopenic purpura in a dog. Can. Vet. J. 1:569-571.

Whitney, J. C. 1967. The pathology of the canine genital tract in false pregnancy. J. Small Anim. Pract. 8:247-263.

Whittick, W. G., ed. 1990. Canine Orthopedics, 2d ed. Philadelphia: Lea & Febiger. 936 pp.

WHO (World Health Organization) Scientific Group. 1986. Primary immunodeficiency diseases. Clin. Immunol. Immunopathol. 40:166-196.

Willis, M. B. 1989. Genetics of the Dog. London: H. F. & G. Witherby. 417 pp.

Winkelstein, J. A., L. C. Cork, D. E. Griffin, J. W. Griffin, R. J. Adams, and D. L. Price. 1981. Genetically determined deficiency of the third component of complement in the dog. Science 212:1169-1170.

Winkelstein, J. A., J. P. Johnson, A. J. Swift, F. Ferry, R. Yolken, and L. C. Cork. 1982. Genetically determined deficiency of the third component of complement in the dog: *In vitro* studies on the complement system and complement-mediated serum activities. J. Immunol. 129:2598-2602.

Winkelstein, J. A., J. P. Johnson, K. M. O'Neil, and L. C. Cork. 1986. Dogs deficient in C3. Progr. Allergy 39:159-168.

Wiśniewski, H., A. B. Johnson, C. S. Raine, W. J. Kay, and R. D. Terry. 1970. Senile plaques and cerebral amyloidosis in aged dogs: A histochemical and ultrastructural study. Lab. Invest. 23:287-296.

Young, D. M., ed. 1979. Part XV: Skeletal system. Pp. 197-264 in Spontaneous Animal Models of Human Disease, vol. II, E. J. Andrews, B. C. Ward, and N. H. Altman, eds. New York: Academic Press.

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DOGS

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